Affecting the Aging Trajectory: *Regulatory Constructs for Gerotherapeutic Drug, Biologic, and Device Development*

Hybrid Public Meeting
Wednesday, May 27, 2026 | 10am - 4pm (*eastern*)

Transcript – Morning

Welcome

Susan C. Winckler, RPh, Esq., CEO, Reagan-Udall Foundation for the FDA

Susan C. Winckler: [00:00:30]

Hello and welcome. Thank you for joining us in-person and online. My name is Susan Winckler, and I'm Chief Executive Officer for the Reagan-Udall Foundation for the FDA, and we are pleased to convene today's public meeting on affecting the aging trajectory regulatory constructs for gerotherapeutic drug, biologic, and device development. The good news is I'm the only one who has to say that multiple times during the [00:01:00] meeting.

For those of you who are new to the Foundation's work, we are the nonprofit, non-government organization created by Congress to help the FDA do more to protect and promote the public's health. Today's meeting is part of that work. We are bringing together experts from across sectors to discuss the relevant regulatory constructs, and this is a meeting about shared learning.

And it's learning that may help inform the agency's work, but it's not a meeting about [00:01:30] regulatory policy development or any specific product. The Foundation does not engage in regulatory decision-making. So I have a few housekeeping notes. We're joined today by about 60 people in the room for a gloriously rainy and dreary day. I'll note we also have a few window washers outside.

So if you sense random movement on the outside, that is apparently intentional. Now, we also have a few hundred attendees participating [00:02:00] virtually. Because of the size of the virtual audience, the virtual attendee cameras and microphones will remain off. We do, however, welcome your thoughts from the virtual audience and so please use the Zoom Q&A function to submit questions and those will get to me here in the room.

For those of you who are in-person, there are note cards that you can use to pass to a member of the staff and they will hand those to me. I will note that we have a minute by minute, second by second [00:02:30] timed agenda. So I will aspire to get to your questions, but we are quite tight on time today. We are recording the event and will post the transcript and the recording to our website.

The bios and head shots for all of our speakers are already on the website as well as a compiled deck of all of the presentations today. The most recent version you can reach through that QR code that is on

the screen. And one final thing, [00:03:00] for those of you who are in-person, we'd ask you to embrace the in-person meeting and not join the Zoom from your laptop at your chair.

So I do want to thank each of our speakers for joining us today. It is just an extraordinary lineup and what I really enjoy about my opportunity at the Foundation is that I get to learn ravenously and today is one of those opportunities. We also thank ARPA-H and the XPRIZE Foundation for sponsoring [00:03:30] today's event and being incredibly engaged collaborators and thought partners for structuring it. So let's take a quick look at the agenda.

We are going to begin this morning by discussing Geroscience and why aging biology is now clinically actionable and how federal and private programs are accelerating that ecosystem. We'll then jump into some of the evidence, what trials have taught us about endpoints, populations, and feasibility. We'll explore the concept of intrinsic capacity and [00:04:00] what those composites have helped, where they have helped predict disability, hospitalization, and mortality.

And then we will hear from speakers who draw on biological aging research to characterize what existing science can support and where the evidence is maturing the fastest. We'll talk about some hypothetical regulatory constructs such as intrinsic capacity and adult health curves along with potential approaches to capture multi-domain aging trajectories. After lunch... That was all before lunch, so [00:04:30] get ready.

After lunch, we are going to hear from the XPRIZE Healthspan teams and three PROSPR Awardees about their work where they will highlight endpoint architecture participant populations and their approaches to interventions. Then we're going to have a discussion with former FDA staff to gather their thinking on how they might have thought about this should the questions be presented to them, and then an industry perspectives panel, and we'll close with [00:05:00] what's going to be a lot of chairs on the stage of individuals to help us reflect on the day and think about future paths forward and potential next steps.

Opening Remarks

Steven Kozlowski, MD, Chief Scientist, Office of the Chief Scientist, FDA

So with that, I will give warning to our first speaker. Dr. Kozlowski, please move on up to the podium. We are pleased to be joined this morning by Dr. Steven Kozlowski, who serves as Chief Scientist in the Office of the Commissioner at the Food and Drug Administration, where he plays a key role in advancing scientific and regulatory [00:05:30] innovation. He is a frequent thought partner for the Foundation and is our primary contact at the agency. Dr. Kozlowski, thank you for joining us today.

Dr. Steven Kozlowski:

Thank you, Susan, and thank you, everybody. So the goal of reversing aging is rather old. Ponce de León searched for the Fountain of Youth in the 16th century. But much earlier than that, in the story of Gilgamesh, which is over 3,000 years old, he searches for the plant of immortality and finds [00:06:00] it at the bottom of the sea. But alas, a snake steals the plant, eats it, and benefits by being able to shed its skin.

Snakes, interestingly enough, have many positive roles. The Asclepius, the symbol of medicine, is a snake. I will say more recent references to snake and snake oil have not been so positive. And I will note that that was actually a mislabeling issue. It was not [00:06:30] safety and efficacy. That remains. So what I do want to talk a little bit about is targeting aging and a general introduction to the topic at hand.

So clearly, targeting aging is more than seeking youth in immortality like these ancient stories. Aging is a key risk factor in almost every chronic disease, yet there are no interventions with regulatory approval for an aging indication. [00:07:00] Aging has not been recognized as a disease or a target for medical product development. And although many, many products and services are marketed sometimes quite extensively with an implication about benefit of aging, there are no accepted regulatory endpoints for an aging indication claim.

Although mortality would obviously be a very meaningful endpoint, it's not a practical endpoint for developing these products. Furthermore, the outcome most meaningful [00:07:30] to patients and with the highest societal impact would be health span, not lifespan. The genetics of aging are an important background and 20 to 30% of longevity has been estimated to be heritable.

However, many studies vary from that particular number with both higher and lower estimates. Nutrition, exercise, sleep, minimizing stress, and not smoking are all lifestyle factors that contribute [00:08:00] to longevity, but not necessarily everybody can optimize these. And even with optimal lifestyle behaviors, there are still genetic limits and there will likely be opportunities to expand these limits with our growing understanding of Geroscience. Now, I want to ask a little bit of a devil's advocate question.

Why not focus on the common chronic diseases of aging, diabetes, arthritis, heart disease, dementia, et cetera? Each of these has its own pathology and may have its own physiological [00:08:30] clocks. Concurrent progress in these would definitely increase health span. The challenge is that each of these chronic disease categories is actually a myriad of different diseases and subtypes, each of which may differ in pathology, in their physiological clocks, and expression in the context of individual patients.

In addition, we likely have expiration dating that is disease independent [00:09:00] and a disease-based strategy would not hit upon that. If there was a more general aging clock, targeting it would have the promise of treating or preventing a large fraction of chronic diseases in the elderly, potentially increasing lifespan and health span beyond current limits. In 1904, the psychologist Charles Spearman proposed a common factor in performance of intellectual tasks.

He called this the g factor. [00:09:30] And the positive correlation among many psychometric tests suggested that 40 to 50% of cognitive performance is driven by this shared g factor. There's controversy around the meaning of this, the validity of psychometric testing and strong acknowledgement that specific cognitive skills are extremely important despite the context or existence of a potential g factor.

However, the question of whether there's a shared general factor [00:10:00] is important, not just for cognition, but very much to aging. Does aging have a g factor? If so, what fraction of longevity and health span are driven by it? Is it polygenic like the psychometric g factor? Even if associated with very complex genetic patterns, is there a shared biological findings? So for instance, in cognition or neuronal fire rate, synaptic density, brain volume.

Are there shared markers for complex genetics biologically [00:10:30] that are part of this g factor? Longevity is also likely to be associated with very complex genetic factors, and thus, shared biological markers would be very, very useful. And thus, there is a great deal of interest in biomarkers for aging. Major categories, they're epigenetic clocks, proteomic, transcriptomic, metabolomic clocks, inflammatory measures, immune markers, senescence markers, telomere measures, [00:11:00] microbiome features, imaging of organs, right?

Many potential possibilities, which we'll probably hear about today. DNA methylation clocks have the potential to potentially estimate morbidity, mortality risk, pace of aging, and may correlate with clinical outcomes like frailty, cardiovascular disease, and cognitive designs. Epigenetic clocks have especially generated excitement with partial or short-term reprogramming of them using variants on [00:11:30] the Yamanaka factors or similar strategies.

How to move these forward? The FDA-NIH BEST resource, Biomarkers, EndpointS, and other Tools, talks about the framework for many types of biomarkers. Obviously, correlation alone is insufficient for surrogate status. For a surrogate endpoint, it must demonstrate that changing it through an intervention predicts an improved clinical outcome. That is a bar that no aging clock or [00:12:00] biomarker has met.

Such an outcome would need clinical evidence. It would need a clinical measure of aging. Functional capacity, which is going to be talked about a lot at this meeting, gait speed, grip strength, VO2, frailty indices, activities of daily living, cognitive performance may be a clinically meaningful aging measure because it reflects the integrated output of many biological systems.

Key functional measures may be [00:12:30] prognostic, gait speed and mortality and hospitalization, grip strength and cardiovascular outcomes, VO2 max and all cause mortality. Frailty indices with adverse outcomes may impact many clinical settings. Functional measures like this are much closer to clinical outcome assessments than biomarkers. They're patient centered directly tied to independence, mobility, cognition, and survival.

If one had a different result between a molecular profile and [00:13:00] a functional measure, that functional measure would clearly be much more meaningful to a patient. The different domains of intrinsic capacity can be evaluated for correlation and aging traits do seem to correlate. This suggests that there really may be a latent general aging factor analogous to the g factor in cognitive science.

Aging may be much more heterogeneous than cognition and could predict very different outcomes with a similar score, for instance, dementia versus cardiovascular [00:13:30] events. Just as in cognition, a general overall score with very specific domain subscores may be the most reasonable approach to this. As I noted, the FDA has not approved a product for aging as a disease indication.

Therapies target a recognized disease syndrome or clinically meaningful outcome, could be frailty, sarcopenia, cognitive impairment, some multimorbidity outcome. [00:14:00] Actual longevity is not a practical outcome and FDA has not accepted biomarkers for reversal of biological age as approvable. No aging biomarker has achieved validated or reasonably likely surrogate endpoint status.

There was a trial of metformin started, the TAME Trial, and it was initiated with a multimorbidity prevention framework, a composite of cardiovascular disease, cancer, dementia, mortality, and

functional [00:14:30] decline. And the investigators note that it was discussed with the FDA. I don't think the FDA has publicly talked a lot about that, but I was at a meeting involving that.

FDA guidance on multiple chronic conditions and patient focused drug development increasingly supports functional patient-centric endpoints. Such endpoints could include mobility, cognition, independence, disability-free survivals, measures that closely align with Geroscience frameworks. [00:15:00] Aging markers are very, very valuable for risk enrichment, mechanistic research, and exploratory trial endpoints, but are not ready to replace clinical outcomes like disability-free survival, dementia, or mortality.

But research in this area is critical. This is an amazing field and really needs to be explored and developed because there's a huge amount of potential opportunities. A discussion I had right before the meeting, you never know when the curve is going to bend, when [00:15:30] you're going to see really tangible results. It certainly is useful to consider frailty, resilience, functional decline outcomes framed as reducing frailty or preserving mobility at this point rather than treating aging, but this is obviously a discussion that will be had.

And functional capacity has already been used extensively in geriatric medicine is therefore very important to consider for aging morbidity assessments. An established [00:16:00] framework or C of A that was meaningful would be so critical in enabling the development of other biomarkers because having some clinical reference point would really be critical for those biomarkers to move into the next steps.

Today's public meeting organized by the Reagan-Udall Foundation in collaboration with ARPA-H and XPRIZE is really going to explore this. Susan has really talked about those things, exploring functional endpoints, thinking about how [00:16:30] to look at that over time, and also what other opportunities there are for patient relevant and regulatory outputs. So thank you very much and I look forward to hearing all the amazing science and concepts that will be talked about today. Thank you.

Susan C. Winckler:

Thanks so much, Dr. Kozlowski, for reminding us about the importance of patient relevant and functional endpoints that also meet a regulatory [00:17:00] standard and for putting a phrase in my head that I probably won't get out, which is expiration dating. So we'll just weave that in somewhere. Okay. Well, yes, in a different context. So let's turn to our experts who are thinking about Geroscience and healthy aging every day.

The Healthspan Imperative: Geroscience, Federal and Private Sector Investment Base

James Appleby, BSPharm, MPH, Chief Executive Officer, Gerontological Society of America
William Greene, MD, Chief Investment Officer, Hevolution Foundation
Jamie Justice, PhD, Executive Director, XPRIZE Healthspan, XPRIZE Foundation
Andrew Brack, PhD, Program Manager, PROactive Health Office, ARPA-H

Susan C. Winckler:

Our opening session will be opened by James Appleby, [00:17:30] who is CEO of The Gerontological Society of America. Dr. Appleby will start us off by focusing on Geroscience, its intersections with other science, and as a pathway to extend human health span rather than just lifespan. Dr. Appleby, please proceed.

James Appleby:

Thank you, Susan, and good morning. I have to say, it's rewarding to see how Geroscience insights are now coming to a stage [00:18:00] where we can apply them to improve all of our lives as we age. This is truly a watershed moment for the field and I think for human health. I should state at the outset that while many are concerned about the cost of aging and the cost of an aging population, aging itself is a blessing.

And I hope that everyone in this room, we're all aging together this morning, I hope we would all agree that aging is a good thing. It enables us to have today, tomorrow, and the next day. How to be thinking about how [00:18:30] we look at aging. Now, the recognition of Geroscience at this point is very timely, and I think that's one thing we should keep in mind that we're in the midst of an unprecedented transformation in the age structure here in the United States, decreasing birth rates, increasing lifespans, changes in immigration, all these things are impacting the age structure.

Most countries, in fact, Western countries have aging populations. And the country that enables [00:19:00] their citizens to thrive, to fully engage, to be productive as they reach advanced age will reap enormous benefits. And I think that's where we are right now here in the United States. Let's see. The big one. Aha, there you go. I have the privilege of leading The Gerontological Society of America.

GSA represents more than 6,500 experts in aging. It's important to note that they're not just researchers, [00:19:30] clinicians, and educators, but they come from 26 different academic disciplines. We think that's particularly important because the complex issues of aging aren't going to be solved from any one discipline together and our members sort of provide that 360 degree perspective on aging.

Our members study all facets of aging and they take a life course approach, again, important for today's conversation, because one of the questions we have to ask ourselves is where in the life course will these new gerotherapeutic interventions be applied? [00:20:00] Now, Geroscience leverages this key insight that the chronic diseases that all of us unfortunately will likely experience as we age have on primary risk factor and that is aging itself, aging itself.

Now, it's important to note that aging itself is not a disease. However, if we can modify aging at the molecular and cellular level using the insights and the biological sciences that are being generated today, [00:20:30] we can slow the onset, delay the onset of all the chronic diseases of aging simultaneously. And that's the real beauty of the Geroscience insight. If you don't take anything else away from our comments today, I want you to know that there's a large group of organizations out there supporting the Geroscience movement.

One of them is the American Federation for Aging Research, and I have on the slide here their website, and I encourage you to check it out. AFAR, led [00:21:00] by Stephanie Lederman, has just done a marvelous job. I know a number of leaders in this room have been very active with them. They've made awards. They do convenings. They do advocacy to really keep a light on the importance of Geroscience and how it can contribute to human health.

Now, the field of Geroscience has developed rapidly over the past 14 years. This gives you a little sense of how it got started. Like so many major innovations in science, it started at NIH and in particular at [00:21:30] NIA where a couple of intrepid researchers, scientists had this idea, "You know what? We should make sure that the entire NIH enterprise understands how aging impacts them."

And they created what's become known as the Geroscience Interest Group. And in fact, Felipe Sierra, who's with us today, was the leader in my mind who really got that started together with this colleague, Ron Kohanski. But this Geroscience Interest Group now includes 21 of 27 institutes and centers at NIH. How often does that happen? [00:22:00] So it's a recognition that others are beginning to realize, "Oh yeah, this aging process is impacting the research that we're doing in our particular center."

The field was nurtured along the way by a series of summits convened at NIH. As you can see here on the slide, it went from initial conceptual frameworking through looking at mechanistic issues, clinical issues. And then in 2023, the most recent summit looking at implementation [00:22:30] of Geroscience through the inequity lens, something very important to the conversation. There is an upcoming Geroscience Summit this December.

It's happening in Bethesda. Registration is open. Viviana, I think, would be happy to talk with you about the details of that and I look forward to seeing you there. Now, as leaders, as we think about the many issues around Geroscience, there were quite a number of opportunities I think mentioned by our first speaker, [00:23:00] but I think there are a number of things we've got to keep in mind as this field evolves. One is communications.

We talk about slowing aging, delaying the onset of chronic diseases of aging, or reversing aging. And I think we've got to be careful the language we choose. While at the molecular level, perhaps some processes are going to be reversed. I think we've got to keep in mind what the public will be seeing. And so therefore, I encourage us to be thoughtful about the language we use because certainly it's clear we can delay the onset of disease, we can slow [00:23:30] aging.

Just be careful about whether or not we use the word reverse. Geroscience is not the same as geriatric medicine. Geriatric medicine, of course, is the care of individuals 65 years of age and older. Geroscience is very different from that. Geroscience will certainly inform that care, but they are different. I noted that there's a question of when in the life course will these innovations be applied?

We think about it with aging, but will they really wait until age 65 to apply them, or will the real opportunity [00:24:00] be in their 30s, 40s, and 50s to apply them? That's something we've got to work out. We're all just younger versions of our older selves. So we should decide when it is we want to start influencing that older self in terms of therapeutics. Geroscience is a multidisciplinary endeavor.

I think this is also important to point out. While today we're going to talk a lot about the biology of aging, the biology of aging interacts continuously with social determinants of health, nonmedical determinants of health, economic security, nutrition, [00:24:30] et cetera. So all experts from all those fields have to be part of the conversation. In summary, the implications of gerotherapeutics, from my mind, are extraordinary.

If we can slow the biological aging process even modestly, just a little bit, we'll be able to extend health span. And so even in incremental improvements such as delaying the onset of disease, frailty, or disability by one year, just by one year, could produce enormous gains for individuals, families, [00:25:00] healthcare systems, and economies. Geroscience offers the possibility that future generations may experience aging differently.

Not perfect aging, not disease-free aging, but healthier aging. My hope is that today's convening will catalyze the development of multiple regulatory pathways, enabling Geroscience innovation to help all of us as we age. And because the geography works for many of the people in the DC area, I will mention that in November, the GSA [00:25:30] Annual Scientific Meeting is next door in National Harbor, Maryland. It's five months from now. Maybe it's a good place to continue these sorts of conversations through workshops, convenings, et cetera. Thank you.

Susan C. Winckler:

Great. Thank you so much, Dr. Appleby. Now we'll be thinking about we are our future selves. Yes. Younger versions of our future selves. That is a good reminder for all of us. [00:26:00] So next up is Dr. William Greene, who's chief investment officer from the Hevolution Foundation, sharing insight on their efforts to catalyze the shift from lifespan to health span. Take it away, Dr. Greene.

Dr. William Greene:

Thank you, and thanks for having me and giving me the opportunity to participate in this very important meeting. So at Hevolution, we're all about bridging the gap between lifespan and health span. You've heard some of the framing, [00:26:30] but I think this is good news. We're living longer. In fact, there's over a billion people in the world today over the age of 60. And by 2050, which suddenly doesn't feel very far off, there'll be more than twice that.

This is absolutely a global phenomenon occurring in economies large and small, countries emerged and emerging, developed and developing. However, [00:27:00] it's kind of been a bad deal. We're living on average about 10 years longer than we were several decades ago, and yet that extra life is essentially taken up by the development of now several complex chronic diseases of aging.

In fact, this health span gap where we live approximately 10 years of our lives with on average more than one chronic debilitating disease [00:27:30] is also absolutely a global phenomenon, easily ascertainable, is affecting essentially populations of every country. As we just heard, age is the number

one risk factor underlying most major diseases today. It's great news that thanks to advances in science, medicine, public health, we're living longer, but now we share [00:28:00] this burden of complex chronic diseases.

And one of the really impactful statistics for me when I joined this field is that spending more money doing what we're doing hasn't made a difference. There's really no clear correlation between how much we spend on R&D, healthcare delivery, or therapeutics and the actual health span gap or the outcomes that we're getting. So clearly new approaches are needed. [00:28:30] The economic impact of this is huge.

In the US alone, we spend over a trillion dollars today treating chronic diseases of aging. And by 2050, it's estimated we'll spend that much treating Alzheimer's disease alone. So this level of healthcare and health and economic burden is also a global phenomenon, and it's challenging pension systems, [00:29:00] healthcare delivery plans and fiscal budgets globally. If we don't do anything about it, there clearly will be crisis breaking points.

So every crisis is an opportunity and the opportunity here clearly is to reduce the burden of age-related diseases. Now, we don't believe at Hevolution that this requires a radical shift in the definition of disease [00:29:30] or fundamentally our biology. What we do believe passionately is that we all need to invest in a shift from reactive amelioration of fundamentally disease symptoms once chronic diseases are established and causing debilitation to a more proactive approach, diagnosing and treating earlier and even getting towards prevention.

As you heard, if we could compress [00:30:00] morbidity by 12 months, we'd reap trillions of dollars in healthcare savings and productivity gains among the people we most would like to be productive. So Hevolution was started to do everything we can to do just that. Hevolution's a global nonprofit founded and funded in Saudi Arabia with an aim to expand healthy lifespan for the benefit of all of humanity.

Our office is in Boston. [00:30:30] And for those of you unfamiliar, here's what Hevolution has done. We've become the largest philanthropic funder of fundamental science in the field with grants to individual investigators, postdoctoral fellowships, scientific partnerships with leading academic institutions. We're the largest sponsor of the XPRIZE Healthspan, which you'll hear more about.

We've convened the world's experts in the largest global convening for health span. And [00:31:00] part of the organization that I'm privileged to work for, we're investing in companies to catalyze this shift to health span. Our investment team is the strategic venture capital arm of the Hevolution Foundation. And in some ways, we look and act like any other life science venture capitalist.

We start companies. We invest in companies. We bring companies to the clinic. We gather [00:31:30] other investors and we drive those companies hopefully to success. What is different about our approach though is we look to develop novel therapeutics that target the biology of aging. How do we do that? We embrace the systems biology of aging. We help our companies to look at pathways rather than targets only.

We engage the most relevant and exciting new data platforms to help us [00:32:00] deconvolute some of those complex platforms into fundamentally straightforward drug development programs. And we

believe that that is entirely possible. We don't believe that we need to redefine aging. We don't believe we need to reverse aging in order to impact health span.

However, we do believe that we need to develop evidence and data that will both enable therapeutics that treat [00:32:30] real diseases in a real way that real doctors can apply to real patients and yet have information about critical endpoints that people care about such as functional endpoints, intrinsic capacity. And what we're doing is investing in our companies to early on in development marry multiomics and deep data analyses of the pathways with functional [00:33:00] endpoints as well as the traditional physiologic endpoints.

So our early stage clinical trials look bigger and are more expensive, but we believe that we're building the foundation for therapeutics that will get to a regulatory process that's rational, get to patients, but drive that shift where we can actually bend the trajectory of these diseases. So that's what we're doing. We're looking forward to participating with all of you in this [00:33:30] important topic and we're here to have a lot of fun doing it. Thank you.

Susan C. Winckler:

Excellent. Thanks so much, Dr. Greene. And we've now heard from the clinicians and the researchers who are working in this space, to those who are investing in catalyzing some of this work. And now I want to turn to Dr. Jamie Justice, who is executive director for the XPRIZE Healthspan part of XPRIZE Foundation. You've been [00:34:00] working in this. We've spent a couple of years talking about the dynamics and the development here, and you've just been a fabulous thought partner for this meeting. So Dr. Justice, take it away.

Dr. Jamie Justice:

Yeah, thank you so much. I want to start by saying a huge thank you to Susan and the Reagan-Udall Foundation for the FDA for your partnership in pulling this off, which is really amazing. And again, this is, and also a huge thanks to many of the people that are in this room, is that this has been the central driving question of my academic scientific career and is [00:34:30] really the central question that we're here to talk about today, which is can a medicine, whether it's a drug, device, biologic, lifestyle intervention, public health measure, can any of these actually affect how we age, change that aging trajectory?

So again, this is something that I'd worked on as a scientist. I'm looking at Nir. I was very fortunate on that arrow that James Appleby showed earlier to come into this field as it was beginning and had [00:35:00] the opportunity to work with folks like Nir Barzilai, Steve Kritchevsky, who you'll hear from later and many others in the room, including George, many, many others that are here to begin to address this question about how do we translate these therapeutics and begin to study this in humans.

So again, I want to bring that trajectory up because this isn't coming out of nowhere as was already pointed out. This is something that we've been working on. The science is developing. It is maturing. We do have now some medicines and therapeutics that are ready for [00:35:30] testing in humans. And so this is where the XPRIZE Healthspan competition comes in. So this competition, again, it's supported. We actually have around 20 sponsors, but our co-title is, of course, Hevolution has been one of the

greatest supports for us and also do want to acknowledge the SOLVE FSHD Foundation and also GSK as being a major contributor to the competition.

And so this is, again, it's a competition model. Just think of it as an alternative funding model to create impact and to develop [00:36:00] solutions. The difference is that rather than a traditional funding mechanism where typical grants are funded upfront is that these actually demonstrate, they put the incentive at the point of demonstration along the way. And so this is a $101 million competition that's non-dilutive capital that goes to teams over different milestone points. And that the key breakthrough that we're asking teams to demonstrate is we have a seven-year global competition to advance proactive, accessible therapeutics that can improve function, and [00:36:30] increase human health span. And so this is human, which means trials. And that's where our teams are coming in now is that we launched in 2023, but we're at a point where these teams are entering trials. And so in absence of regulatory guidance, we as a scientific field and community have been forced to ask, if a medicine could improve how we age, how would we know?

And so we don't have this sort of central G factor that we talked about earlier. There's [00:37:00] no general intelligence even though I would love to see that develop. And so knowing that we don't currently have the evidence base, think about this as a competition that we can use to build the foundation to create the evidence that's needed to get there. And so we had to make very explicit decisions in pursuit of this competition to actually put money towards this. If something worked, what would convince us as scientists? What's meaningful to the general public? What does that patient voice [00:37:30] look like? Is it just an epigenetic biomarker or is there something meaningful that we should be pursuing to show that there may be some clinical benefit that would actually be helpful and that we could actually drive the field to create that resource?

And so for the XPRIZE Healthspan competition, we have spent the last couple of years addressing exactly this. This year, starting in August, we'll have 10 or more finalist teams that will start one year clinical trials. At the end of this period, [00:38:00] we'll be awarding teams that can demonstrate that their therapeutic treatment restores muscle, cognitive and immune function. So this is again, function-based, multi-endpoint, and that there has to be administered in people who are 50 years or older and that therapeutic must take one year or less. In terms of money, I'm not going to harp on that right now. I think what's important for this is that we are proposing alternative trial designs where teams actually have to meet response thresholds within [00:38:30] individuals and they have to surpass expected declines that you would see. So again, we're looking at the aging trajectory and how we can deviate from that trajectory to show that they are showing improvements, not just slowed or declines, but actually improvements that would equivalent to 10, 15 or 20 years in a reference population. We also have a grant program out right now with some folks in this room and online who are developing those thresholds with us.

Again, one of the key things here isn't [00:39:00] going to be awarding the money, which will be nice, but one of the key attributes is that we're developing resources and prospective longitudinal data sets across multiple therapeutics from global participants and teams. And so again, for judging, we're looking at immune function, cognitive function, and immune function. We have additional measures for safety, clinical characteristics, and harmonization efforts with things like intrinsic capacity to make sure that the dataset we provide [00:39:30] is of maximum utility.

We have a couple of core partners that teams have to use. Jamie Dwyer is in the audience today, who's the PI for our data coordinating center that's at the University of Utah. So these are prospective trials

with data that's centralized that will be adjudicated centrally. We also have central labs and biobanks so that we can develop some of these molecular and other biomarkers and that we actually have the same yardstick applied to all teams. This is a great source for development for the future. [00:40:00] Again, that central lab and biobank is the UCSD led by doctors Michael Corley and Anthony Molina. And again, this is intended to be a future resource so that we can do that kind of biomarker discovery, meta analysis, patient selection, surrogate endpoint evaluation. We see this as one of the more critical resources that we could build is we do need a surrogate endpoint, but how do we get there? We need to get there by actually providing the data and doing this, as Bill said, is to not [00:40:30] do this reactive, but in a proactive, thoughtful process to move forward.

And so I'm really delighted to share this with you all and hand it over to who's not a partner, but a dear friend and someone that we've worked hard to align with and very much support the efforts of others.

Susan C. Winckler:

Great. Thanks, Dr. Justice. As I think about the work you described, [00:41:00] it seems like an incredible investment in the infrastructure not only for your participants, but then the broader ecosystem could learn from and continue to develop. So let me turn to the next podium, which has our next speaker. Dr. Andrew Brack is program manager for the PROactive Health Office from the Advanced Research Projects Agency for Health, which we would refer to as ARPA-H for the rest of the meeting, if that's okay. So Dr. Brack, take [00:41:30] it away.

Dr. Andrew Brack:

Thank you. First of all, it's a great honor to be here. It's been a real privilege to work with Susan the Reagan-Udall Foundation and with Jamie as XPRIZE, we try and move this field towards regulatory readiness. And so just a bit of background on ARPA for those who are not familiar. ARPA was created to really change the course of human health to solve significant healthcare problems where the solutions are too risky, too interdisciplinary for sort [00:42:00] of normal traditional grants or industry alone. ARPA funds breakthrough capabilities, the sort of high risk coordination heavy, platform building work that makes an entire field executable. We work across silos. We don't fund just academics, we fund academics, small companies, pharma, and work with regulators to find the solutions for the American people. And when ARPA releases a program, it is a signal. It's a commitment that we are going to build in that area of healthcare.

[00:42:30] So we do this by building audacious programs that are prioritized for speed. Speed is a key thing that we build in every program and every performer is in the room will know that. We're knocking on doors, we're asking where's the stuff? Because American people shouldn't have to wait. We're trying to build medicines to help them.

And so why now? So ARPA leans into exciting areas that are ready for acceleration. And aging is one of those. Aging scientists are ready developing preclinical work. There's early [00:43:00] therapeutics, which we think could work in humans. What's holding the field back and why we're here today is to turn those ideas into clinically tested, regulatory ready, scalable medicines. And so that's where we bring up PROSPR. As America's population grows, sort of the costs, as Bill mentioned, both financial and personal. PROSPR is the first program from ARPA-H focused on extending health span. And the agency is committing real money. $144 [00:43:30] million up to 144 million, I should say, across seven teams to

address this problem. And so to this end, and we've been talking about endpoints, PROSPA will identify predictive and intervenable surrogates of hard endpoints to test therapeutics targeting aging directly in clinical trials. So the program is only three years old, but multiple performers will soon be seeking formal input from the FDA.

[00:44:00] And so just a little bit about PROSPR. So my team and I built PROSPR because there's no clear path to target aging itself. However, running a clinical trial to intervene in health span extension is so far non-viable. It takes too long, costs too much money. So PROSPA is going to accelerate the translation of health span extending therapeutics by leveraging what we've been talking about already, intrinsic capacity, as a composite measure of feel and function. And so we can see that in the center of the slide [00:44:30] there. So intrinsic capacity is a conceptual measurement framework developed by the World Health Organization. It's a composite measure that makes you, you may be familiar with some of the measures, it's walking speed, grip strength, cognitive function. These measures have face validity. If they move in one direction earlier, you know it. What makes IC compelling is that it focuses on the capacities that let people remain mobile, independent, and engaged in daily life.

As people age, their health and function declines. Intrinsic capacity precedes that [00:45:00] and captures that decline. Moreover, it's not anchored in a single disease. And it's not limited to late outcomes like mortality or dependence. So it offers a way to think about multi-domain functional health earlier in the aging trajectory, that proactive health that Bill was mentioning, but it does not mean that IC is fully validated or ready to serve as a universal endpoint. It's not. But we think it's one of the most promising places to start if the goal is to build clinically meaningful frameworks [00:45:30] for Geroscience, trials. PROSPR is therefore working to do three things, generate evidence for interventions that may preserve health during aging through lifestyle interventions as shown on the left-hand side here, drug repurposing approaches and next generation therapeutics. The second and probably equally important, if not more important, is helping to build a clinical pathway for health span surrogates.

A path that can include fit for purpose use of endpoints, better trial designs, and early engagement [00:46:00] around regulatory use. And that's why today's conversation matters so much. Later today, you're going to hear about some of the conclusions from a consensus meeting, that was held on intrinsic capacity organized by ARPA that was held last month. That white paper should be available by the end of the day for everybody to download. You're also going to hear from several PROSPR performers, one team on their efforts in putting together a clinical outcome assessment application for intrinsic capacity. I think probably that's going to get submitted of a pre-letter of [00:46:30] intent today, and two biotech teams on their effects for novel small molecules for targeted engaging and drug repurposing approaches for health span trials. And so I'd just like to thank you all for being here for this important conversation, and I'll pass you back over to Susan.

Susan C. Winckler:

Fabulous. Thank you, Dr. Brack. Another part of that ecosystem that we are building here or seeing being built. [00:47:00] So let's turn to our second session. If you are thinking I have not seen nearly enough data and graphs and the things that we would expect in a scientific meeting, get ready. Now we are at that time.

Landmark Evidence: What Aging Trials Have Taught Us About Endpoints, Populations, and Feasibility

Nir Barzilai, MD, Director, Institute for Geroscience, Albert Einstein College of Medicine, President of the Academy of Geroscience
Stephen B. Kritchevsky, PhD, Professor, Gerontology and Geriatrics Internal Medicine, Wake Forest University School of Medicine
Joan Mannick, MD, Chief Medical Officer, Altos Labs
Eric Morgen, MD, MPH, FRCPC, Chief Operating Officer, BioAge Labs

Susan C. Winckler:

And so in this session, we are going to hear about the evidence and what prior trials have taught us. Our speakers are going to draw on prior current and emerging biological aging research to characterize what existing science can support and where it's evolving. Dr. Nir Barzilai [00:47:30] is going to kick us off. You serve as director of the Institute for Aging Research at the Albert Einstein College-

Dr. Nir Barzilai:

Institute for Geroscience.

Susan C. Winckler:

Ah, better. Yes.

Dr. Nir Barzilai:

We've changed all the names.

Susan C. Winckler:
Excellent. And so we will fix that on the slide deck and you're president of the Academy of Geroscience. Thank you and please proceed.

Dr. Nir Barzilai:

Thanks. And Susan, first of all, I think for many of us, it feels like a moonshot, like a small step, but [00:48:00] unlike the moonshot, it's going to be much more important for humankind what we're trying to do. So thank you for your efforts.

And for Steve, this was such a great review. I was wondering how much the FDA can speak about it and you give us the opportunity to actually start to turn the curve like you said. So by the way, this is the new logo of the academy. A lot of the geroscience are going to have a logo [00:48:30] of an hourglass that we're trying to stop. Here's my DNA and get the youthful part up top.

The academy is global academy. We have hundred of the best scientists and leaders and 10% of them are in this room. So thank you. So thank you very much. I'll do the introduction first because I think we all have done that. Aging has a biology. [00:49:00] We know who's young and who's old. We actually know that people age at different rates, right? And that's why I came to the field because of this

flexibility. But I think what people don't realize and what is our really main job to do is that aging drives diseases. Okay, this biology drives diseases. It's not that we get sick and we get old. No, we get old, and that's what drives diseases. You can be born with homozygosity for upper E4, which means [00:49:30] that you have high risk for Alzheimer's, but you're not born demented and you're not demented at 10 years or 50 years, you need the biology of aging and I can go like that for every disease.

But the importance is that we have to stop or to target aging before we get diseases. This is our goal. And we'll talk about targets and you're right, we're trying to delay aging and there are cases that we can stop and reverse [00:50:00] them. But the revolution, really the revolution that we are offering is to optimize our health, spending time on our health rather than the diseases. That's really what geroscience will able to provide.

Okay. So now I'll make very important point. First of all, and Steve, to your answer, what are the mechanisms? You're right, if we had diabetes, the FDA will say, "So what are you doing? You're insulin secretagogues, you're insulin sensitizer, you're losing [00:50:30] weight, right? So what are the mechanisms of aging?" And what unites us in geroscience is those hallmarks of aging. To be a hallmark of aging, you have to show that something has changed with aging and you can actually in animal take young animal and make them old, but more important, you can take old animal and target this hallmark and they'll be healthier and they live longer. That's how you become a hallmark.

And we currently have [00:51:00] 12 hallmarks and I'm not going to spend any more time except saying two things. You target any one of the hallmarks and you get benefits. And the reason you get benefit is because you actually change other hallmarks. So I want to say the hallmarks are not really all the mechanisms of aging, but they're really good target because you target [00:51:30] one of them and you get the other. One of my problems as a president is not to allow any hallmark go in the middle because everyone of the hallmark can say, "Hey, we are the center because when we fix this, we fix everyone." And that's the case for everyone, but this is the mechanism. That's how we look at the mechanism of aging.

So what does it take to say that something is a geritherapeutic? So we think there are really four [00:52:00] things we have to show. First of all, on preclinical, we have to show that our medicine changes the hallmarks of aging. And I'm talking on a cellular level. Okay? Take cells and show that they're changing because the hallmarks are cellular hallmarks of aging. That's one thing. The second thing we want to show that when we give it to old animal, they live healthier and they live [00:52:30] long.[inaudible 00:52:30] Restriction. Okay. GLP-1, right?

Please understand statins are very important drugs. If you have high cholesterol, it prevents heart disease. It prevents cardiovascular mortality, by the way, not overall mortality, but statins do not change the hallmark of aging, and you give statin to animal, they don't live longer. What statin means to me is, yeah, it's important to prevent [00:53:00] heart disease. You go straight to Alzheimer or to cancer or to something else. Okay? We're talking about different kind of [inaudible 00:53:07].

Okay. On the clinical level, what do those drugs want to show? You want to show in a clinical study that you give this drug versus placebo and it prevents not only the disease that it was... Or treat, not only the disease that it meant to treat, but multi other morbidities. And also overall mortalities, [00:53:30] not the disease specific mortality, an overall mortality. And if you're asking, do we have such drugs? Absolutely. So let me make the case for that. What we've done first of all is decide to take all the FDA

approved drugs that seem to investigators that they change hallmarks of aging and they actually test if those animals live longer.

[00:54:00] So the six points are for geroscience and the other six points are, well, those drugs have been in clinical trials, what does it show? And you have here all the drugs, nevermind what's in blue, but those in ping are the ones who get 11, 12 points on this scale. And they are, by the way, SGLT2 inhibitors, those who cannot see, metformin, bisphosphonates, GLP receptor agonist.

[00:54:30] I want to make a point because some of those drugs are diabetic drugs, but they target hallmarks of aging. And how do we know that metformin, for example, which has metabolic properties, but it is shown in a clinical trial that it prevents 50% hospitalization and 50% of a death in COVID and 60% [00:55:00] less long COVID. And it immediately shows you metformin has immune effect, inflammatory effect, and maybe the resiliency of a body to withhold it. That's a non-diabetic population. So just keep in mind all those are targeting the hallmarks of aging.

So let me make some points. This is SGLT2 inhibitors in the ITP, which is a way [00:55:30] to in a multi-central study to show if it extend lifespan in animals. And I'm not going through that, but it extend lifespan of animals. But more important, what happens in humans? And I just want to tell you, I'm an active diabetologist. I'm attending fellows once, twice a month. And I've used SGLT2 in my clinic for almost 10 years, almost decade. And when we started using SGLT2, we all [00:56:00] knew that in the clinical trials, it didn't only improve diabetes, it prevented cardiovascular disease and kidney diseases. It took years, but then the cardiologist said, "Hey, maybe that's something that's relevant to us." So they did a study, some diabetics, some non-diabetic, and they showed that it prevent diabetes and it prevented kidney, disease and not only improved cardiovascular outcomes.

And then later the nephrologist came and [00:56:30] said, "Hey, what about us?" And this is an example of one of the studies in New England Journal of Medicine where, let me see if it works here, where I'll just take you through the graphs, where basically they took 4,000 people, a little bit more than 4,000 people over 32 months, placebo control, mainly non-diabetic. And they looked at the right, the upper part, [00:57:00] the left is overall data, but the upper part is specific renal outcomes and they were decreased by 40% over this time. The one C in the middle on the bottom is cardiovascular outcomes also decreased by 40% and on the right, all cause of mortality is also decreased by 40%. In other words, there's [00:57:30] clinical evidence and it's circular. You say, "Okay, but this is kidney." Okay, so I showed you heart, I showed you diabetes.

It's all the same data because what they do, they target aging. And I can go over examples on health span, SGLT2 and cardiovascular and renal and metformin and heart failure and bisphosphonates on cardiovascular disease and SGLT2 on renal outcome and the same about SGLT2 [00:58:00] on all causes mortality, metformin on atherosclerosis mortality, bisphosphonate on ICU mortality, GLP-1 on overall mortality. There's a lot of other things. So the question for the FDA, why it's legal to use this drug? Why not repurpose those drug for aging? It's been done for metformin for a long time.

So this is my last slide. I know you're standing [00:58:30] and connecting everything you heard and connecting it to PROSPR. What we've done is we took those clinical studies that I showed you some of. We took and got blood and plasma from those studies, studies that had outcomes, from control and from people who were treated with the drugs.

And we are [00:59:00] going to do multiomics, everything, thousands of things, proteomic and metabolomic and methylation and everything. And in each case, we're going to say, A, what are the biomarkers of aging? But more important, which of them have changed with therapy? Now, every drug will change whatever biomarkers they had, but we think that together somewhere in the middle in the hallmarks of aging, [00:59:30] we're going to see a consensus, a consensus for all those drugs that will really accelerate how we're going to come forward. So thank you.

Susan C. Winckler:

And we will watch for those results. Thank you so much, Dr. Barzilai. We really appreciate that grounding. And so now for those of you who are in the room, we're going to turn to a series of virtual speakers. Some had aspired to join us in person and were thwarted [01:00:00] by various things. This happens these days with travel and any other number of complications, but we're pleased to be able to bring to the virtual stage Dr. Stephen Kritchevsky, who's Professor of Gerontology and Geriatrics Internal Medicine, Wake Forest University School of Medicine. This is my AV check. Dr. Kritchevsky, we can see you and I believe we'll be able to hear you. Please proceed.

Dr. Stephen B. Kritchevsky:
Okay. I'm going to keep talking and if you can't hear me interrupt, okay? [01:00:30] So that's fine.

Susan C. Winckler:

We can hear you and the team will put your slides up right now.

Dr. Stephen B. Kritchevsky:

Okay. Are they up? Okay. Yeah. So I've been working in this space for a while along with Jamie and Mark Espeland and Nir and George Kuchel and several others trying to figure out how to bring this idea of geroscience [01:01:00] to some kind of testing and randomized clinical trial setting that people would believe that, and we would convince ourselves that we really could affect the biology of aging to improve human health.

You've heard already several speakers talk about the promise of that. [01:01:30] One of the things in trying to develop these projects for peer review is to fight against the current biomedical paradigm, which is that the strategy for prevention has to do with controlling specific risk factors for specific diseases. As you heard Nir speak about the statins, this is good for one disease, and a very, very useful paradigm. And really the FDA evaluation process is really built around this [01:02:00] thought where the geroscience paradigm is that we can delay aging itself and delay multiple age-related disease and the regulatory framework to allow these kinds of experiments and trials to go forward is not as well-developed.

So what is the endpoint? And Jamie already put this question, if you had an intervention that slowed aging, how would you know it? [01:02:30] And part of the problem in this field is that there are a lot of people with a lot of ideas about this, but there really hasn't been elucidated very well. And so everyone has their own private idea about this. And so when people are in review situations, you get people bringing a lot of different perspectives. So we did some focus groups at Wake and we asked [01:03:00] the focus groups, these were made up of experts, including geriatrician, subspecialists, statisticians,

pharma-based scientists, and regulatory specialists this question about a hypothetical drug that slowed aging and what should the outcome be? And there was some agreement and some disagreement, but mostly I wanted to focus on the points of agreement. They agreed that the outcome should reflect [01:03:30] several dimensions of health, that it should reflect participant goals and their desired outcomes include patient reported outcomes be recognized by the FDA or other regulatory authority. And we're in a bit of a catch 22 there and that's really the point of this whole day. They would have to be tailored in a general view that biomarkers are insufficient for the task. It has to be things that are [01:04:00] measurable or sensible.

One outcome that seems to fit many of these criteria is something called a deficit accumulation or frailty outcome. And what that is a list of age-related health problems you could have and you get a point for everyone that you do have and [01:04:30] basically your frailty is the ratio of the ones that you do have to all the ones you might have. And the attraction of this approach is that as people age, we really don't know exactly which age-related disease they're going to get. We know they're going to get age-related diseases. The specific ones we can take a guess at based on other risk factors, but really we're really unclear [01:05:00] They're really uncertain. Having an index, this index is open to all age-related causes so that if you're at risk for one set of diseases, this will increment as you get age, but for another person, some other things will increment. So it provides coverage across all the age-related problems that one might have.

This is data where this outcome was modeled in the [01:05:30] Look AHEAD study, which is a randomized trial of intensive lifestyle intervention, including weight loss versus an attention control. In over 5,000 people with type two diabetes, the intervention itself ran for about nine years. But when you look at the index, the intervention was immediately impactful on the index, and that benefit has been sustained for 20 [01:06:00] years or almost 20 years over the course of the study and is of a magnitude that would be consistent with slowing aging by about one year.

So there are other ways that people have looked at this. If you're in model organism field, they tend to focus on all course mortality because that tends to be what they study. There is a geriatrics perspective, which is [01:06:30] disability-free survival, which has been used in the ASPREE trial and is currently in the ongoing PREVENTABLE trial. And under this perspective, things like the frailty phenotype, which is slightly different, intrinsic capacity and resilience all poking here.

When we were designing the TAME trial, we picked a multimorbidity perspective, a reduction in the rate of new disease accrual. And the Look AHEAD [01:07:00] has also modeled this and showed that that information also slowed the accrual of new diseases. And then there's a deficit perspective that I just introduced.

Finally, there's the patient perspective and we also did focus group with older folks who have been in studies at our institution and they're very much aligned with the geriatrics perspective. Older adults fear being dependent on others and not being able to do for [01:07:30] themselves. So they're very interested in maintaining physical and mental capacity.

So in the TAME trial, we had this design with the clinical outcome, but we had many, which is the time to incidence of any of a basket of age-related diseases that you didn't already have when you came into the study. We also were planning a secondary and tertiary outcomes to look at [01:08:00] decline in mobility and cognitive function and change in biomarkers of aging. I think it's helpful for the group to hear what kinds of pushback we got in NIH review of the trial. There's questions, would metformin have

the same effect on each component? Worry that the most common endpoint would drive the result. One reviewer said, "Well, you need a separate trial for each component, which kind of defeats the purpose [01:08:30] here." And then finally, if you got a positive result, you wouldn't necessarily know if it was through an age-related mechanism. So just to people be aware that although we are enthusiast, the world out there has some other thoughts about a lot of this stuff.

So composite endpoint is where we're headed towards, I think with either a lot of the things that we're discussing. [01:09:00] Advantage of a composite is that with components, the number of components increasing, the event rate can lead to shorter trials or smaller sample sizes. A disadvantage is if the intervention benefits don't accrue to all the components, you end up with a lower effect size and maybe lower power.

So we tried to apply all these lessons. We're planning a trial called [01:09:30] HALO, which is to be a five-year trial of caloric restriction in older adults and we decided to go with the deficit accumulation effect but be spoken for obesity and weight. So we used these five criteria to select index components that they had something to do with weight and there was some evidence that an intervention on weight would lead to [01:10:00] their reduction. This led to these index components about 14. And I wanted to just quickly review the indexes. It captures a wide range of benefits, helps in clinical communication. It's easier to recruit than for a single disease or disease class, smaller sample size than for individual diseases. And it's also congruent with the idea that caloric restriction slows aging. [01:10:30] With that, just realize that there's a continuum of things that we could measure. FDA interest has mostly been into the left side of this graph and we're trying to square the circle. I hope we get there with the discussions that are stimulated today. Thank you.

Susan C. Winckler:

Thanks so much, Dr. Kritchevsky. Very helpful in recapping or in reminding us what [01:11:00] has been done as well as what's on the horizon. Our next speaker is also joining us virtually. Dr. Joan Mannick is Chief Medical Officer at Altos Labs. Dr. Mannick, please provide your remarks.

Dr. Joan Mannick:

Thank you so much, Susan. I'm going to talk today about improving immune function in the elderly as a sort of different regulatory construct for gerotherapeutic drugs and lessons we've learned from clinical trials of mTOR inhibitors. [01:11:30] Just for disclosure, I'm actually working now at Altos Labs, but what I'm going to talk to you was all done at either Novartis or Retro Bio, and I'm delighted David Glass is in the audience because he worked together with me on this program at Novartis. Improving immune function in older adults is something that we don't think a lot about in drug development in biotech and pharma, but it actually may have pleiotropic [01:12:00] health benefits and even target multimorbidity. If we could develop a drug that improved immune function, it's likely to decrease the incidence and severity of infections to improve vaccination response, but also we now know that the immune system is important for cancer immunosurveillance so we might be able to decrease cancer incidents with such a drug.

We know the immune system clears cells that build up [01:12:30] in aging organs, which are called senescent cells and those cause organ damage, so clearing them could have benefit. And then there was a really important study done by Laura Niedernhofer's group published in nature several years ago that

showed if she just aged the immune system in mice multiple other organ systems age suggesting the immune system actually might drive aging in animals and potentially in humans. [01:13:00] What could we do to improve immune function in the elderly? Well, one thing we might be able to do is use drugs that target a protein called mTOR because inhibiting mTOR has been shown to improve immune function in aging mice. A study was done in very old mice where they were given six weeks of an mTOR inhibitor, in this case rapamycin, and that six weeks treatment had a variety of benefits on [01:13:30] immune function, it resulted in improved influenza vaccination response.

Back in 2010, we started a program at Novartis where we said, "Could we use mTOR inhibitors to improve immune function in older adults?" And this was a little counterintuitive because mTOR inhibitors are actually used to suppress immune function in organ transplant patients, but we used very low doses or intermittent doses of [01:14:00] mTOR inhibitors that were predicted not to suppress immune function. And in fact, when we gave older adults six weeks of an mTOR inhibitor, they had improved influenza vaccination response. And not only did they have improved vaccination response, but when we looked at the adverse events reported in the trial, the people getting the low doses of mTOR inhibitors were reporting having fewer respiratory tract infections of all types, not just influenza. [01:14:30] We did a second trial and we said, "Not only can we see if the mTOR inhibitors improve influenza vaccination response, but we'll also prospectively collect infections to see if mTOR inhibitors decrease all cause infections and we'll do gene expression profiling to see what are the genes whose expression change in people getting mTOR inhibitors."

And again, we found that low doses of mTOR inhibitors enhanced influenza vaccination response, but [01:15:00] they also significantly decreased the incidence of respiratory tract infections, most of which are viral. And then we started to get a clue as to why this was happening because the main genes whose expression changed in people getting mTOR inhibitors were critical antiviral genes that are used by the immune system to fight viral infections and this response tends to be deficient in the elderly. Then we did a third trial and we said, "Let's just see if [01:15:30] we can decrease the incidence of respiratory tract infections in the elderly if we dose them for 16 weeks during winter cold and flu season when the elderly have the most respiratory tract infections." And we did find again the low doses of mTOR inhibitors decrease the incidence of respiratory tract infections and upregulated antiviral immune responses.

We thought, "Great, maybe what we're developing here is a drug that will enhance antiviral [01:16:00] immunity in the elderly and protect them from respiratory tract infections." At this point we went for an end of Phase 2b meeting at the FDA and for the Phase 2b trial, the FDA had requested an endpoint of percent of subjects with lab confirmed respiratory tract infections. Everyone had to have symptoms consistent with a respiratory tract infection and a nasopharyngeal swab that identified a pathogen. But for the Phase 3, the FDA said, " [01:16:30] We have to learn with you. This is new to us developing a drug that decreases the incidence of all types of respiratory tract infections."

This was right before the COVID-19 pandemic and they said, "In the real world, nobody gets a nasopharyngeal swab when they get a respiratory tract infection so you can't use that in your endpoint. Instead, what people care about are their symptoms when they get respiratory tract infections. You have to show that you can decrease the [01:17:00] percent of subjects with symptoms consistent with a respiratory tract infection irrespective of whether they turn out to actually be due to an infection." This turned out to be a very messy, noisy endpoint because older people have a lot of respiratory symptoms that meet the criteria of a respiratory tract infection even when they know they're not sick with an infection.

That trial did not meet its endpoint, which was disappointing, but we learned a lot of important lessons for the field. [01:17:30] First of all, we learned that using intermittent doses or low doses of mTOR inhibitors were well tolerated in the elderly. That was a big concern when we started this program that you couldn't target these fundamental pathways that regulate aging biology safely. Second, we learned that low doses of mTOR inhibitors in every trial that we looked, even that failed Phase 3, significantly upregulate antiviral immune responses. [01:18:00] Third, we learned that this upregulation of antiviral immunity may have a bigger effect on severity of infection than incidents and so we probably weren't using the right endpoint in our previous Phase 2 and 3 trials. And last, the efficacy seemed to be greatest in people 75 and above. And the sense we got is that a lot of people between age 65 and 75 might actually have a normal [01:18:30] antiviral response where it isn't until older ages 75 and above where a deficit in the immune response gets more homogeneous and you can see a greater benefit from boosting antiviral immunity.

With all these lessons learned, we decided to do one last small trial that we never published testing a different endpoint based on these lessons learned. And we said, "Let's look if low doses of mTOR inhibitors can decrease the severity [01:19:00] of a lab confirmed infection in a very elderly population." What we did was we looked at whether low doses of mTOR inhibitors could prevent the severity of lab confirmed COVID-19 in a nursing home population. This study was done at the beginning of the pandemic before COVID vaccines were available and it was done in nursing homes under lockdown. When there was a COVID-19 outbreak, people were either randomized to get a low [01:19:30] dose of an mTOR inhibitor or placebo. And here were the results. It was a very small trial, but people who were randomized to placebo, 23% got severe COVID-19 and half of them died. The people who got the mTOR inhibitor, no one even got a symptom of COVID-19. It's a really small trial. It has to be repeated, but it suggests we're starting to hone in on the right kind of endpoint for this drug and this indication.

Just in conclusion, I think enhancing [01:20:00] immune function in the elderly may be a viable regulatory path for gerotherapeutic drugs, but it's really important to establish regulatory endpoints that are more feasible with the FDA. I think the incidence and severity of respiratory tract infections is actually a feasible endpoint because the incidence of respiratory tract infections is so high, you don't have to have a really long and large trial for this endpoint, but it's critical that lab confirmation [01:20:30] be used as part of the endpoint, not just symptoms. And last biomarkers that guide selection of older adult populations with deficient immune response I think will be very helpful for future clinical trials. Thanks very much.

Susan C. Winckler:

Thank you so much, Dr. Mannick. Really helpful to provide us a different perspective, a different look at ways to potentially intervene here as well as the results and messy endpoints might be another [01:21:00] phrase that we begin to pick up and think about through the day, but as well as those endpoints that are relevant to patients. To close us out in this section where we're looking at what we've learned from prior trials and efforts and how we might think about that going forward, we're going to turn to Dr. Eric Morgen, who is the chief operating officer at BioAge Labs. Dr. Morgen, we can see you, so go ahead.

Dr. Eric Morgen:

Great. Yeah, it looks like my audio's on. Thanks very much for having me and it's [01:21:30] great to be speaking to you all today. Yeah, so you can see where I'm from, I will enhance the slides here. Drug

discovery for healthy aging. What I'm going to talk a little bit today is who we are at BioAge and a philosophy for drug development and discovery for healthy aging, give a couple examples from our lead program of how this works, and talk about [01:22:00] some of the incentives in this industry and also talk about an effort to help align those incentives better for promoting the health of older adults.

At BioAge Labs, we are harnessing the biology of human aging to develop new therapies for metabolic diseases. That talks about the perspective we have, which we feel very strongly that the process [01:22:30] of aging biology causes vulnerability across multiple organ systems, which eventually manifests in all of these chronic diseases, which affect older adults. And we want to target that fundamental aging biology, but we want to do development for specific diseases, in this case, metabolic diseases. This is an overview of our pipeline so you can see what we're doing. We're developing a number of different drugs. Our lead program is BGE-102. [01:23:00] This is an anti-inflammatory drug, an NLRP3 inhibitor, and I'll talk a little bit more about this one later. That one's going into, recently finished the Phase 1 trial is going to Phase 2 trials this year.

Our next program is APJ, which is a drug being developed for obesity and also muscle biology. We have earlier stage programs that we're not disclosing at this point. And then we have a target discovery collaboration with Novartis. And so a big part of what we do at BioAge [01:23:30] also relates to our data platform where we look at human data to find aging targets and I'll talk a bit more about that as well. Moving on.

This is that underlying philosophy that I told you about that it's really one of the highest impact things we can do in drug development broadly across the industry is target mechanisms that are fundamental aging mechanisms because treating one disease just doesn't help that much in this goal [01:24:00] that we all, I think underlying everyone really understands, which is how long you're healthy. We all want to be healthy longer. And the benefits of being healthy longer are not only for individual patients, they're for for societies and healthcare systems that are strained right now by the burden of chronic disease and fixing or ameliorating one disease really just doesn't help that much with the length of time where you're healthy and where you're not a burden on all those systems. The potential for addressing [01:24:30] those underlying mechanisms is really strong and I'm going to go slightly out of order here.

And so what we want to do is target mechanisms that are fundamental human aging mechanisms. And so we've put together a platform to do that because the key question is, well, what are those human aging mechanisms? And I don't have a separate slide about it today, but it's quite precedented as like other speakers have mentioned that there's a lot of great animal models where it's been shown that various interventions [01:25:00] can delay the onset of ill health with age across multiple organ systems. And so if you can do it in model organisms, why not do it in people? We're here to do it in people, but what are those targets? Because we all know that animal biology translates incompletely or in some cases not at all to humans.

And so we put together this human platform where we take advantage of the natural variability in the human population. You can see this age of death graph and there's a wide variability in the age at which people [01:25:30] get their initial disease, chronic diseases, and then ultimately decline and die. And so we can look at what the biological differences are between people who are very robust against all this decline and they live very healthy into old ages versus people who have a more traditional trajectory of decline and death at an earlier age. And we do this by taking banked samples of people who have been tracked for many decades as part of existing studies and we take blood samples out of the freezer for those people and we profile them using modern omics [01:26:00] technologies to really get a deep

picture of the biology. And then we do modeling to figure out which of these pathways seem likely to mediate resistance versus vulnerability to this aging trajectory, these fundamental aging mechanisms.

And so once we have one of those, we develop drugs against it and we embark on a clinical development plan. And the way we do it and many other people in the field as well do this is this disease first focus. We ultimately are trying to reach this big peak on the [01:26:30] right where we're treating aging. And what does that mean? To me, it really means disease prevention, that you'll be able to prevent multiple or ideally many or all of these aging related diseases and delay their onset. And that really extends health and improves quality of life and improves working lifespan and all these societal and individual benefits, but there's no direct pathway to get there. There's no regulatory pathway, no payer pathway, et cetera.

And so what we do is we take a disease first focus. Once we have one of these aging [01:27:00] mechanisms out of the platform, we develop it for very specific diseases where the mechanism makes a lot of sense against that disease. There's a high unmet need and market opportunity. The tension here, of course, is that all of the value of the right-hand peak is mostly not captured in the development program where you're initially targeting whole diseases. Investors don't really see that value because those trials are very long, very expensive and sort of distant in the future in this paradigm.

[01:27:30] And so this is just the example of our lead program, just to give you a very quick sense of how this works. We get all sorts of data out of the platform showing that NLRP3 activity in this case, greater activation in a middle-aged person that NLRP3 really has this striking progressive effect on mortality risk over time. There's many other pieces of data, some of which are summarized at the bottom, but I won't go into them. And we have some [01:28:00] literature happens to have some great causal evidence and knockout models in mice that you increase survival by knocking out this gene.

And so we've taken that drug, as I said, we've completed Phase 1 trials where we've shown that it decreases a key efficacy biomarker, which is CRP. It's an anti-inflammatory drug and CRP is the most well accepted marker of chronic inflammation with age that leads to diseases like atherosclerosis. And so we've shown our drug here [01:28:30] reduces CRP by 80 to 86%, an excellent early signal. In this disease first focus, we're taking this into a couple of diseases first. As an anti-inflammatory mechanism, there's really a very broad array of diseases this could go into specifically for NLRP3, many inflammatory diseases, et cetera, but also it shows potential in atherosclerosis prevention, so that's CBD here. And [01:29:00] then our drug has a property that gets into the brain and the eye. In addition to being able to treat things like Alzheimer's or potentially address those, we can also address eye disease. And so we're going into trials this year for cardiovascular disease and for diabetic macular edema.

That's the BioAge story and I touched earlier on this tension with incentives. And I think that clinical development on [01:29:30] drugs for aging actually is underincentivized dramatically relative to the potential because as I said, what we as patients, putting my patient hat on here, what we don't want is to take a drug that makes the disease a little bit better and then we still get a bunch of diseases over time. What we want is to stay healthy. I made this point earlier, but I'm making it again. And that's also what the healthcare system, payers, governments want. They [01:30:00] want people to be productive longer, taxable longer, and to not be a drain on the healthcare system longer. And so how do we change those incentives?

And I'm just going to briefly describe here a great proposal by the Kitalys Institute for a new FDA pathway that they are calling the THRIVE Act. It's a new pathway for health span drugs. And there's a lot

of detail, but I'll summarize it at a very high level because I'm nearing the end of my time here, but basically [01:30:30] it defines a health span product as any drug that increases health span, a length of time that you're healthy. And increases health span is specifically defined as preventing or reversing two or more age-related diseases. And so the idea is that if a drug is active against two distinct age-related diseases, that it's likely doing it by an aging mechanism. This creates a new FDA indication called health span essentially that doesn't exist today, does not change any existing pathways [01:31:00] and addresses these points in blue that I mentioned that basically it's inherently harder to run trials for prevention endpoints and particularly multidisease prevention.

And the incentive here is that if a drug is essentially near approval, has good clinical safety evidence, and great evidence of some kind may be animal evidence to show that it has potential across multiple chronic diseases that it could get early market access. Around the time you'd be getting your first approval [01:31:30] for a specific disease, you would also be able to market the drug for health span. And this would be time limited. You'd then have five years to show much better evidence that this is actually happening. And then if you got that, then another five years to really show definitive evidence of prevention across multiple diseases, but you'd now have the money to do that for your market access. And of course, if you don't meet those timelines, you're off the market.

This is just a good idea I wanted to share [01:32:00] and I'll just end with a slide that's optimistic here because it's an exciting time to be working on these kinds of things. There's a lot of organizations trying to push this area forward, including XPRIZE Healthspan, Longevity Biotechnology Association, trying to define what it means to work in this field of longevity biotechnology, people working on the biomarkers of aging. A4LI is a group trying to advocate for these issues in Congress and they've created a longevity science caucus and the CATALIS Institute, [01:32:30] which produced the Thrive proposal. It's a great time to be working and I'm optimistic about future pathways that could really incentivize the kind of drug development that I think society needs.

Toward Regulatory Constructs: Intrinsic Capacity, Adult Health Curves, and Multi-Domain Endpoints

David B. Allison, PhD, Chief of Nutrition and Director, USDA's Children's Nutrition Research Center, Baylor College of Medicine
John Beard, MBBS, PhD, Irene Diamond Professor, Columbia University Mailman School of Public Health
Kelly Anderson, PhD, Scientific Engineering and Technical Advisor, ARPA-H
Nicholas Schork, PhD, Director, Quantitative Medicine & Systems Biology, HonorHealth Research Institute

Susan C. Winckler:

Excellent. Thanks so much, Dr. Morgen. I know you were all paying attention when he defined productivity as being taxable and I think we're looking for something other than that in the regulatory endpoints that matter to people and [01:33:00] regulators that we're aiming higher. Let's pivot from learning about some research that has been done before to talking about potential precision management approaches, some endpoint architecture, and thinking through a little bit more in depth for four more presentations before we break for lunch to think about capturing multi-domain aging trajectories. Our first speaker is Dr. David Allison, who is Chief of Nutrition [01:33:30] and Director of the

USDA Children's Nutrition Research Center at the Baylor College of Medicine. That podium is open, so feel free to use it. Welcome.

Dr. David B. Allison:

Thank you very much. Well, it's truly a pleasure to be here with you today. I'm honored by the invitation and I want to say thank you to all the supporters of this and the supporters of my research and the work I do with others, including and especially the NIA for the Nathan Shock [01:34:00] Center Coordinating Centers where I lead the data analysis aspects. I'm going to talk a little bit today about what the endpoint might be and I will talk about composite endpoints like intrinsic capacity, but I'm going to focus a little bit more on mortality, which I think really is something we need to pivot to. We hear a great deal of pontification in the field, things that are ipse dixit [01:34:30] statements, a Latin phrase meaning because he himself said it. What is your evidence for this? The evidence is I said it.

And so we hear obesity as a disease, excuse me, aging is a disease. Aging is not a disease as though there were an answer to this question, as though there were a defined set of criteria we all agreed on of what a disease is that we could point to and say, "This is an empirical question." We can say is something a hydrogen molecule or an atom [01:35:00] or not because we have a clear definition of that and then we can compare something to the definition. There's no universally agreed upon definition of a disease and there is no definition that brings in all the things we conventionally want to bring in and excludes the things we want to exclude. Is Pluto a planet? Sometimes it is sometimes it isn't because planet is a social construct and so a question of is [01:35:30] aging a disease is nonsense and I mean that in a literal sense. It is non sense. It can't be answered. It's not a real question.

A real question is should we consider aging a disease? Should we declare aging a disease? And that's a social judgment. We did the same thing with obesity. We declared it a disease. We didn't prove it that it was a disease. There's no experiment you can do and say, "If I get [01:36:00] this answer, it's a disease. If I get that answer, it's not." If you can't specify the experiment, whether you can do it or not, if you can't specify the hypothetical experiment even, then you don't have a scientific question. You have a social or some other kind of question. That's very important because then we're going to get into things like markers of a disease, markers of aging. And we've heard several times of people say, we just heard a moment ago, [01:36:30] if you affect two separate diseases, then you have affected aging. I don't even know what aging is.

I think that we need to recognize that no definition of a composite will be satisfying. I prepared a lot of specific slides on this. Let's see if I can figure out how to do this. Here's some of the different endpoints. I'm not going to read this because I think many people have said things like this [01:37:00] already. The point is there's no universally accepted criterion. And if you don't have a universally accepted criterion, then you go to issues of, have you really got the thing you're looking for and whether you think you do or not, will you convince enough of the rest of the world who matter for it to be important? If we're not talking about being like Isaac Newton who developed [01:37:30] the universal laws of gravitation, for example, or the calculus and stuck it in his desk drawer for a while, because he said, "Science is just about me and I don't owe it to anybody. I'm a Trinity professor here."

We are doing science for humanity and so no matter how good you think it is, if it doesn't affect anything else in the world, it wasn't a good use of the resources you were entrusted [01:38:00] with. We have to ask what's going to be convincing. If you are the Coast Guard and you say, "We have a new program to increase rescues of people who are drowning and we get to them fast." You say, "Okay,

what have you accomplished?" "Well, we have faster boats. We have better trained staff. We have divers and swimmers who are faster, [01:38:30] stronger and have better VO2 max." Okay, how many more people did you pull out of the water who were drowning? I don't care how fast your boats were. And so I think we just need to recognize that that's where we're going to be with this.

I think what does it take? We're going to need statistically significant effects. And again, this goes back to the social point. We can talk about Bayesian analyses and be good. We should do [01:39:00] some. The rest of the world mostly is still thinking Frequentist. We probably need to design trials around endpoints where we can do Frequentist statistical significance testing and get P values that are two tailed and less than .05 at least. We need clinical relevance. The FDA says what matters is how people feel, function, or survive, [01:39:30] and I think that makes good sense. Who really cares what their blood pressure is? Who really cares how many transposons you have? Who cares you're telling me your length. I care how I look. I care how I feel. I care about what I can do. I care about how long I live. Some people think we shouldn't care about how long we live. It doesn't matter. I don't care how long we live. As long as up until the end, I'm healthy and vital and not dependent. And I'd say good.

Do you all feel healthy and vital, not dependent right now? [01:40:00] Okay. How about I kill you right now? Then you'll have a life that was 100% healthy and vital. I don't know if anybody's going to volunteer for this. And what it says is that maybe that pontification is not really what people want. Maybe people would like to live longer and maybe even if I lived a little bit for a while, maybe I still like to stay alive. I think we need to really look at lifespan I think as vital. I think furthermore, everybody knows what it is. [01:40:30] We can debate about measures of intrinsic capacity and composites, and that's very important. We can debate about it.

And if we can debate about it, convincing this is gone. Because if Dr. Barzilai, for example, publishes a paper and says, "We have slowed aging by this composite," and he lists his pre-registered composite with 10 variables and he dutifully puts his raw data out in the public domain for rigor, reproducibility, and transparency, and then I get the raw [01:41:00] data. I say, "I don't agree with that one. This is my composite." And give me a big enough computer and enough time and I will find a credibly looking composite that gives a different answer. And now where is credibility? Where is convincingness? I think that we need to use these kinds of variables but not rely on them. What I think we need to rely on is mortality rate. Why? We've [01:41:30] already heard why longevity itself is not viable. None of us want to start a trial in 20 year olds now, have them followed for 70 year olds and long after everyone in this room is dead, find out the answer and find whether we have something to help the public. We want to do something sooner. Mortality rate can be done sooner.

Now the question is, if we randomize people to treatment or control, for example, and then we look at mortality rate in a five-year interval, let's say, [01:42:00] does that really equate to longevity? The answer is it doesn't have to. There's no mathematical proof that it must, but under some conditions it will. It becomes a little bit empirical. My colleagues and I did a study some years ago where many of the people in the room gave us their rat and mouse data. And what we found was that if we took full longevity studies and we cut them off at two years, would we have gotten on average the same answer [01:42:30] as if we did the full life span? And the answer is yes, almost always. Now it takes a lot more rats and mice about five times more if you do that, but you do get the same answer approximately. Scott Pletcher has shown similar things in flies. If you affect mortality rate in a certain way, then you pretty much affect longevity in that way. This has been shown in some human studies.

[01:43:00] Can we substitute it? The answer is there's no mathematical proof that in any on situation, a certain observation of mortality rate must equate to longevity. But at some point you say, if it looks like a duck and it walks like a duck and it quacks like a duck, for practical purposes it's a duck. And so what I would say is if we can do a randomized controlled trial in which we start people at [01:43:30] multiple different ages, let's say it's a five-year study, start them at 20, 21, 22, 80, 81, all the way up. And in every age we start, we get a very similar reduction in mortality rate. And we've also looked at this in a rat or a mouse where we can look at the whole longevity and the mortality rate in a brief period relates to the longevity. And if we see in study after study of rodents of many substances, this [01:44:00] occurs, which I think we will. At that point, I think you can say for practical purposes, we have shown that this thing affects longevity.

These are just some extra slides, some assumptions. In conclusion, I would say that no current proxy is fully convincing. Longevity is the gold standing, but a practical mortality is measurable, mechanistically linked to lifespan, and consistent with longevity across [01:44:30] multiple models. And I therefore I think that's what we should do. And so let us take this path through the woods as Jean-Jacques Rousseau said. And if you'd like to debate with me, and I hope you would, come down and visit us in Texas and we'll go out on the trail together or out in the fishing boat and then we'll have some barbecue and we'll talk about this. Thank you.

Susan C. Winckler:

All right. Thank you so much, Dr. Allison. That's teeing up our conversation and thinking creatively in this space. [01:45:00] Our next speaker is virtual and so we're going to turn now to Dr. Beard, Dr. John Beard, who serves as the Irene Diamond professor of Columbia University Mailman School of Public Health. Dr. Beard, we can see you. So go ahead.

Dr. John Beard:

Good morning, everybody. And it's great to be with you, I'm sorry I can't be there in person. I'm going to talk to you about a topic that's already been raised a few times this morning, intrinsic capacity. But before I do that, I thought I would just explore [01:45:30] why I think we need a new way to measure health. And you've already heard this morning around the advances which we've had in geroscience and how we now understand that the health problems of older age arise from an ongoing complex biological process that accumulates across time, across the life course, and basically increases the risk of not just one chronic condition but multiple chronic conditions at the same time. And what [01:46:00] we need to do, as Jamie said at the very beginning, is understand that if we have some interventions which target some of these processes, how would we know if they made a difference?

And I think one of the challenges that confronts us is that health is actually a continuum and we need to be able to detect subtle changes in health very early if we're really going to be able to intervene and make a difference. And the problem is that most of the measures we currently use to measure health, disease, [01:46:30] disability, even frailty measures or mortality, these are very late stage manifestations of these processes that have occurred across the life course. And they also take a long time to emerge, which is very difficult for clinical trials because you have to run them for a long time before you get an outcome. At the same time, we are seeing massive amounts of new data coming from wearable devices and all sorts of biomarkers that are being discovered. [01:47:00] And for the first time in history, we now have the analytical capacity through artificial intelligence to actually interpret that complex data and understand it.

Okay. Sorry, having problems moving my slides. Okay. How might intrinsic capacity help? Well, somehow we need to link these biomarkers and the things we may observe at a biological level to a clinically meaningful outcome, something that makes [01:47:30] a difference to you and to me. And the outcome that's reported by older people as their priority is functioning more than the presence or absence of disease and even more than life extension. So this construct of intrinsic capacity is a measure of individual level functioning and it's also a continuous measure and that allows us and potentially could allow us to measure incremental change across the entire life course. Where did it come from? [01:48:00] Its origins were in the World Report on Aging and Health, which was released in 2015. This was a report that tried to orient global action on aging and health around the building and maintaining of functional ability rather than the presence or absence of disease. And the report framed that functional ability as arising from two different things, one is the individual and all the individual level attributes, functional attributes.

The other [01:48:30] is the environment that that individual inhabits and things in that environment, for example, assisted devices like glasses, which enable us to be and do things, but which aren't really the focus of geroscience, the individual level attributes, the report labeled intrinsic capacity. So after the report was released, there was a conceptual paper which identified [01:49:00] five pivotal subdomains of intrinsic capacity. And these are pretty obvious things that you would expect. Cognitive capacity, the ability to think, locomotive capacity, the ability to move, sensory capacity so vision, hearing, taste, psychological capacity. And vitality for which there's still a lot of ongoing debate, but which basically frames the capacity to retain capacity in the face of internal or external stressors. And crucially, [01:49:30] this structure was then validated empirically in multiple large population-based studies and demonstrated to be a powerful predictor of future mortality and care dependence after accounting for age, sex, socioeconomic status, and multimorbidity. So this is validated in terms of its long-term relationship with significant outcomes. If you [01:50:00] look at trends in intrinsic capacity within the population, again, what we all know is that capacity tends to decline with increasing age.

Here you have a figure, the top left-hand corner is overall intrinsic capacity and then the other boxes are each of the subdomains. And you see for the last half of life here between 50 and 100 years, a steady decline at a population level in intrinsic capacity for both men and women with [01:50:30] women experiencing slightly lower levels of capacity than men at the same age. And this has actually been very useful at a population level in answering some challenging questions. So the one key question has always been, we know people are living longer, but are we living longer and healthier or are older people today experiencing worse health than people did in previous generations? This is a figure from a study in the English longitudinal study of aging [01:51:00] looking at trajectories and capacity for different birth cohorts born in the 50s, 40s, 30s, and 20s and so on.

And what you can clearly see is significant improvements in those trajectories and so from that study, we concluded that 70 really is the new 60 when you look at it from a functional perspective. So intrinsic capacity is useful at a population level, but what about at an individual level and for clinical care? Well, in fact, we already [01:51:30] use an analog in pediatrics. This is a figure, a photo of me and my young son a few years ago and as my son developed, we would follow his development, his progress on these normative curves. What we proposed was maybe as I start entering a period of decline, maybe we should be able to follow my trajectory in the same way to see where I sit on the normative [01:52:00] distribution and identify if my trajectory is veering off what the normal trajectory would be and then to ask why and what can we do about it.

And this is actually already being done as a way of aligning trajectories of care with trajectories of capacity. In the Integrated Care for Older People program, also developed by the WHO, which uses a screening assessment of capacity to identify people with deficits who [01:52:30] then have more intense assessments and it then leads to an integrated care and coordinated care program aligned with the aspirations of each individual. So where might we go now? Already we have an ICD code for intrinsic capacity for age-related declines in intrinsic capacity. And I think that's a really useful starting point and it demonstrates that it's possible [01:53:00] to codify this in some of the standard research and classification approaches which we already use. But how do we formulate this as an outcome for clinical research and care? As a couple of speakers have already mentioned, I think there needs to be a lot of work on the measurement approaches which we use.

We still don't have total coherence on the structure, what this subdomain of vitality [01:53:30] actually represents. And also many of the measures we've used have been used opportunistically because they've been in studies which were already undertaken and so they're not designed for purpose. So for example, measures of cognitive capacity might include the Mini-Mental State Exam, which is really an assessment to see whether somebody is developing dementia or not. What we need is much more subtle measures which can detect early change, so we need improvement on measurement. We also need to think [01:54:00] about how we can link the biomarkers that many people are starting to talk about to these changes and moreover, can we develop biomarkers of intrinsic capacity itself? That would mean we don't actually have to do performance tests because we have some biological way where we do, for example, a blood test, which gives us the same information.

But I think the biggest challenge, and it's probably a challenge that's going to confront FDA and all of us as we look to how this might be applied in research [01:54:30] and in clinical practice, is that medicine is currently built around thresholds, not continuums. Doctors are trained to identify when people pass a threshold and can be identified as having a condition that requires treatment. That's very different to actually following people over time and trying to build and maintain the best possible trajectory of an outcome. And I think it will require a significant paradigm shift both for [01:55:00] clinicians and also for researchers. So I'll leave it at there and I think I even stayed within my time.

Susan C. Winckler:

You did brilliantly, Dr. Beard.

Thank you for that introduction and challenging us to think about the potential for an adult health curve. I have to quip, I wonder whether my adult son heard you, he recently presented me with a tube of anti-inflammatory cream and said, "Your knees are only going to get worse. [01:55:30] Use this and you'll feel a lot better." So he might've been listening in. We're now going to turn to, there was some work that actually Dr. Brack mentioned this morning about trying to dig a bit more into this idea of intrinsic capacity. And so Kelly Anderson from ARPA-H is going to tell us about that process. Dr. Anderson leads the scientific engineering and technical advisor... She plays that role rather at ARPA-H. So Kelly, thanks [01:56:00] for joining us and tell us about that consensus work.

Dr. Kelly Anderson:

Thank you, Susan. All right. So you just heard about what intrinsic capacity is and how it can be measured in a variety of ways, but so far there hasn't been a consensus on how IC and its domains might

be measured and used in geroscience trials in a way that's practical, clinically interpretable, and relevant to regulatory discussion. So that's why ARPA-H convened [01:56:30] a consensus meeting on this topic last month. Before I get into the consensus itself, I want to briefly address why we focus so much attention on intrinsic capacity rather than on lifespan, mortality or even frailty. In some settings, these may be entirely appropriate, but for gerotherapeutic development, they might be too late or insensitive as an endpoint, especially in relatively healthy or pre-disease populations. Most people will feel loss of functional capacities well before age-related [01:57:00] diseases manifest. So what we need is a clinically meaningful way to detect whether an intervention is preserving the capacities that let people live well.

That's where intrinsic capacity becomes attractive. It gives us a multi-domain clinical framework that may allow us to detect meaningful therapeutic effects earlier potentially with fewer participants while still building the evidence that links those changes to harder outcomes over time. To get community input on what's viable [01:57:30] now, we convened a multidisciplinary group of experts that included geriatricians, geroscience researchers, clinical trialists, biostatisticians, IC experts, industry and regulatory facing experts, and importantly, both advocates and skeptics of IC as a trial endpoint. The majority of experts came in with prior experience, either with intrinsic capacity itself or with one or more of its component measures in human trials or studies. That mattered because the goal was not really to have a theoretical discussion, [01:58:00] but to identify where there's already enough convergence to support a practical version one framework and where more evidence is still needed. I should say at the outset that what I'm presenting today is only a short summary of a much more detailed 40-plus page consensus document. That document includes the supporting rationale, the areas where the group agreed and areas where there was less agreement and the proposed validation next steps.

One of the most important [01:58:30] outcomes of the meeting was clarity around what this framework is and what it is not. The group did not propose that intrinsic capacity is already ready as a validated surrogate endpoint and it didn't recommend a single global IC composite as universally ready to be a primary endpoint. IC is also not proposed to replace later stage frailty or disease specific endpoints. Instead, the consensus position was that IC version one should be understood as a standardized multi-domain clinical [01:59:00] outcome framework. Its purpose is really to help the field generate more consistent and comparable evidence and to support constructive dialogue with regulators about fit-for-purpose contexts of use. The initial focus is in older community dwelling adults with early decline in intrinsic capacities but who remain largely independent and disease-free. In that community IC can be used most credibly now as a multi-domain clinical outcome, especially through domain-specific measures, pre-specified [01:59:30] secondary outcomes and enrichment strategies.

A central conclusion from the meeting was that at the present stage, the most supportable approach is to focus on the domains of intrinsic capacity rather than on a single aggregated score. As John just described, IC includes five major domains of function. The group felt that these domains are more clinically interpretable scientifically, clinically, and potentially from a regulatory perspective than an overall IC score is today. [02:00:00] A key point of discussion was the distinction between a single domain effect and a broader multi-domain geroscience effect. There was general agreement that an improvement in one domain may be clinically meaningful and useful in its own right, but not enough evidence to support a broader effect on aging across systems. That distinction is important, but it doesn't diminish the value of domain specific outcomes because aging can affect different systems on different timescales demonstrating benefit in an individual [02:00:30] domain may still be highly

relevant, for example, in supporting the use of a therapy for age-associated decline in the cognitive or locomotor domains of intrinsic capacity.

The most practical output of the meeting was the proposed core IC trial battery version one. The goal was not to identify the perfect measures for all future studies, but rather to identify a set of measures that are feasible, clinically interpretable, reasonably scalable, [02:01:00] and familiar enough to be implemented in trials now. For the locomotor domain, the recommended measures were gait speed and the short physical performance battery with explicit discussion that modified or continuous forms are preferable to reduce ceiling effects where possible. For cognition, the recommendation was a global screen like MoCA paired with a processing speed or executive function measure because those domains may be particularly sensitive to age-related change. For the psychological [02:01:30] domain, the group felt that depression alone was too narrow and that some coverage of anxiety or distress should also be included, ideally with some wellbeing captured where feasible. For the sensory domain, the minimum package was visual acuity and a basic hearing assessment while recognizing that more sensitive measures like contrast, sensitivity, speech and noise, and even olfaction may be valuable in future refinements.

And for vitality, which remains the least mature domain conceptually, [02:02:00] the recommendation was not a single fixed test, but a small set of measures reflecting reserve and physiologic balance like grip strength, respiratory function, fatigability, et cetera. Thus, the IC battery represents a trial-ready starting point that can be tested now. The group also address where IC appears most usable in gerotherapeutic trials. The first area is enrichment and stratification. Baseline IC domain [02:02:30] scores may help identify participants at higher risk of subsequent disability or loss of independence and can help structure randomization or subgroup analyses in a more informed way. The second area is as pre-specified secondary outcomes. This is especially important in the near term because it allows trials to capture broad functional effects while building a shared evidence base across studies. The third area is domain specific primary endpoints. In particular, the group [02:03:00] felt that locomotor and cognitive domain composites may be reasonable primary endpoints in programs where there's a mechanistic rationale and a clear expectation that the intervention could affect that domain over the trial time horizon.

In terms of scoring and interpretation, the group emphasized simplicity, transparency, and interpretability. The recommendation was that each IC domain should be measured, analyzed, and reported separately to allow investigators, [02:03:30] clinicians, and eventually regulators to see clearly which domains moved, whether effects are consistent across domains and whether any harms or trade-offs are being obscured by aggregation. If a global IC score is used, the provisional recommendation for version one was a simple, normalized, unweighted composite. That was not because equal weighting is known to be optimal, but because it's the most transparent and least assumption heavy place to start. That recommendation [02:04:00] provides a way to begin accumulating comparable data while more is learned about weighting responsiveness and interpretation. The group also emphasized that meaningful change should initially be interpreted at the domain level where possible, especially in areas where the existing literature can help anchor interpretation to clinically relevant change.

Looking ahead, the consensus view was that this framework should now move into a stepwise validation phase and this is where [02:04:30] PROSPER can play an important role. One immediate next step is retrospective work in existing cohorts and trials. Since most of the IC measures are already commonly used in human studies, IC domains and simple composites can be constructed and evaluated against outcomes like disability, loss of independence, hospitalization, and mortality. A second step is

prospective implementation in geroscience and health span studies so that the version one framework can be tested in real interventional settings. That includes [02:05:00] evaluating responsiveness, sealing and floor effects, and the extent to which individual domains or broader multi-domain profiles change over realistic trial periods.

And finally, we see this work as part of a broader effort to support a credible evidence generation path for eventual regulatory use in geroscience and health span trials. In the near term, that means generating more disciplined evidence around how patients feel and function, clarifying fit-for-purpose contexts of use [02:05:30] and beginning those conversations with the FDA early while data are still being generated so that development can proceed in a way that's aligned with regulatory expectations rather than retrofitted later. Overall, we view IC version one not as a final standard, but as a practical framework that can help the field move from concept toward more consistent trial ready and ultimately regular relevant evidence. Thank you for allowing us to share this with you today.

Susan C. Winckler:

Great. Thanks so [02:06:00] much, Dr. Anderson. So we have one more presentation before lunch and lunch is already ready. So no pressure, Dr. Schork, I'm going to turn to you in just a second and then we will move in the afternoon just as a preview, we have a lot more conversation. So this has been our slide intensive morning that we will close out now at the last presentation from Dr. Nicholas Schork, who is Director of Quantitative Medicine and Systems Biology at the HonorHealth Research Institute. [02:06:30] Dr. Schork, go ahead and take it away.

Dr. Nicholas Schork:

Okay, thank you. It's really flattering to be asked to participate today. I'm going to actually get into the weeds a bit on some of the points and concepts that David, John and Kelly brought up. First of all, I want to acknowledge some of my input from colleagues that I've had in the last little while, including Jamie Justice and the XPRIZE team. I come with a different perspective. My perspective is, as [02:07:00] Eric Morgan had described, very patient focused. So my background is designing clinical trials for genetically mediated disease, say, rare conditions. Also have a very big focus on clinical translation, asking questions like will this intervention benefit the participant? And lastly, have experience in phase one oncology trials where the drugs are tested in the early phases of development on actual patients, [02:07:30] not healthy volunteers. So my design elements that I want to focus on today really are rooted in these sorts of experiences.

Now, something else that I want to bring to people's attention is a paper published about 35 years ago by former FDA Commissioner Rob Califf with Eric Topol, someone I worked with for about seven years on the distinction between mega trials and mini trials. And they describe mega trials as those that can provide definitive evidence about the mortality [02:08:00] or morbidity reduction afforded by a class of therapy so that broad changes in clinical practice can be justified. In contrast, mini trials can explain why a treatment is affective to allow development of more effective approaches attacking the identified mechanisms. There's other complementarity. For example, there's an understanding about how mini trials could inform the use of, say, drugs in broader contexts. So many people [02:08:30] would argue, well, these mega trials will expose where mini trials need to be pursued. I'm thinking just the opposite. We might want to pursue mini trials to motivate mega trials, especially in the context of repurposed drugs of the type that are being thought of as having geroprotective potential.

And real world evidence and evidence synthesis should be taken into consideration here when thinking about how to develop novel approaches to vetting geroprotectors. So [02:09:00] in this context, we know that drugs do not work in everybody and that includes some candidate geroprotectors out there like GLP-1 receptor agonists or even dietary restriction. So we need a different paradigm for trials, on that gets away from doing a large study only to find out that many people don't benefit and then looking for the reasons why people don't benefit. I think maybe we could put that on its head and study individuals, aggregate the results of studies on those individuals, [02:09:30] and then learn what works better for each individual based on, say, profile characteristics that they might have. So a related question is how can we define response? And John brought up a number of points that I want to embellish a little bit. So we could focus on things like mortality rates, morbidity rates, but the question is, how do we actually leverage them to define meaningful clinical endpoints?

I think you could define response [02:10:00] criteria, as pointed out earlier, a priori, before the study begins by leveraging data, say, on age reversal or life tables, clinical assessments that one might deem important and in that way, set up the trial so we have more responder, non-responder outcomes. The belief being that we want to see a small response rate in the control group and a large response rate in the intervention [02:10:30] group. And just to point out some commonality with some emerging regulatory guidance, there was a document issued about the use of Bayesian methodology in clinical trials. So defining response thresholds a priori has elements of a Bayesian approach to clinical trials consistent again with this very recent guideline from the FDA. Okay. How do we leverage these response thresholds? [02:11:00] Well, if we had an individual enroll in a trial who's aged 60 and he tested a certain way for, say, memory, we could define a response that would be clinically meaningful and meaningful in the context of, say, age reversal by asking what they should manifest if they improve by 10-year units or something like that.

And we could do this using historical and legacy data, we're actually doing this as part of the XPRIZE. As I mentioned before, [02:11:30] defining what a reasonable and clinically meaningful and statistically meaningful response might be a priori and then using those to count responders, non-responders going forward in the actual trial. And you could use intrinsic capacity in this manner, either in domain specific ways or as a composite. Now, as pointed out earlier, intrinsic capacity has many components to it, the five different components. I would argue [02:12:00] that means we're looking at a multivariate phenotype. So statistically, one could actually test the hypothesis that these different components are actually improving as a result of provision of the geroprotector in mind. And if the multivariate hypothesis is true, that is your drug does influence all these phenotypes, then using a multivariate test is more powerful than testing each phenotype individually. I won't go into the weeds here, [02:12:30] just show that the solid lines depict the power of multivariate tests and the dash lines, univariate, the serial correlation and other things affect these curves, but I won't go into detail about that.

Just point out that David Allison, a previous speaker in this session, and I had a paper on similar topics about 30 years ago, proving the point old dogs, old tricks here. Okay. So I'm an advocate of single case experimental designs and aggregating [02:13:00] the results of those to make sweeping claims about population utility of an intervention. So the way these work is you collect more data on each individual to see how the drug is affecting them rather than less data on more people. And there's many advantages to these trial designs. I won't go into, again, the details. Suffice it to say that if you're collecting all this data on an individual patient and say your drug is not shown to benefit them, then all that data you have [02:13:30] on your patient could actually benefit them in the way clinical practices run. So we think that these trials have a twofer benefit, learn a lot of interesting biology and benefit the patient in the process.

And here we just show some power curves comparing designs that have many individuals on few measures versus fewer individuals on many measures. And if you're interested in looking at variation and response, [02:14:00] then the designs with more data collected on fewer individuals, more longitudinal data collected on fewer individuals are more powerful to detect response differences. So should keep that in mind in designing studies for drugs that we know are likely to vary. There are many, many other trial designs that could be brought to bear on testing geroprotectors. I will not go through this. A recent paper by Paul Franks describes these in really elegant detail, but there are other [02:14:30] trial designs that could be thought of, say those that leverage new approach methodologies. Again, we've seen new regulation come out or new guidance come out from the FDA about the adoption of NAMS in, say, clinical trials.

Again, won't go through those, just to point out that these should be on people's radars. One other thing that was recently announced that I think the community should embrace in terms of guidance from the FDA has to do with the implementation of real-time clinical trials. I'm [02:15:00] going to go in a little bit of detail about those in a minute, but suffice it to say that in the document describing this, the FDA members describe different aspects of the trial design and where some new approaches could be incorporated. I believe that for example, real-time trials could be used in all phases of clinical development, not just in phase two as described in the document. I do believe that these [02:15:30] novel alternative methodologies could be used at earlier stages in clinical trials, not just in the preclinical stage. I think Bayesian statistics can be, again, used in all phases, not just stay in phase three.

And I think real world evidence could be brought to bear on more than just post-marketing surveillance. Now with real-time clinical trials, the intuition is you test the drug on an individual and see if they're a responder. So using the threshold criteria we talked about before [02:16:00] and just count up the number of responders and non-responders that you see over time. And if you accumulate enough evidence that the response rate is passing a threshold, then you can declare victory as opposed to having a fixed sample size throughout your trial. And in this way, you could save enormous amounts of money but draw the same statistically compelling conclusions. So something to think about. Last thing I'll think about, which is a little bit more aspirational, is actually developing [02:16:30] systems to aggregate data to accumulate evidence over time. So for example, there's many people who are proposing the development of prediction models for the express purpose of dictating who should get one drug.

Now with all those models, we'd have to vet them somehow. So I'm arguing that for some subset, we actually subject them to one of these NF1 or SCED trials, see if they responded in the way that they were predicted. If they did or didn't, we feed that information back into the training set for the prediction [02:17:00] models, always improving the system. This is known as a learning system. I think these things have practical utility and should be taken seriously. I'll just point out that this was proposed back under Rob Califf's aegis in the FDA about 10 years ago with a companion paper that came out during Scott Gottlieb's time as commissioner arguing that maybe clinical trials of the type we're describing now in systems should have [02:17:30] a merit or should be considered to have merit. And again, this was 10 years ago, so I will stop there and let you guys enjoy lunch. So thank you.

Susan C. Winckler:

Thank you so much, Dr. Schork. Helpful for us to think about what we can learn from other just developments generally in clinical trials and opportunities to improve them and how it might apply in

this space. So with that, let me note that we will reconvene in this room at 1:05 PM, which gives you [02:18:00] 42 minutes to eat lunch. We will see you then.