Kinexions

Insights for Translating Life Sciences into Solutions

A Note from the CEO

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A Note from the Chairman

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Welcome to the Winter 2021/2022 edition of *Kinexions*!

The highlights of this issue are excerpted transcripts and summaries from several of the amazing sessions from our *Targeting Metabesity 2021* conference in October 2021. The full conference contents are an embarrassment of riches, including perspectives from eminent speakers (in addition to those of former FDA Commissioner Stephen Hahn and Scripps' Eric Topol) such as former Human Genome Sciences CEO Bill Haseltine, investor and

Janus, the Roman god of beginnings, gates, transitions, time, duality and doors, is often used around January as a pictophor for both looking forward and looking to the past. And, because past is prologue, plotting the future is often benefited by understanding the past. 2021 was a year of [to us] unprecedented change in climatic, social, political, technical, and scientific spheres. Much of this seeming cataclysmic change can be put into perspective by expanding the time scale to include the Ice Age, Prohibition in the US, the American and English Civil Wars, and the invention of the printing press. No doubt the

philanthropist Esther Dyson, National Academy of Medicine President Victor Dzau, leading Boomers age wave expert Ken Dychtwald, and many others...

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pace of change is accelerating, but let's admit that no generation has been—or ever will be—free of disconcerting, if not existentially threatening, change...

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Clarifying Regulatory Pathways for Longevity Products


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The need for clear regulatory pathways for healthspan products is one of the most pressing issues in the explosively growing longevity space.

At *Targeting Metabesity 2021*, Kinexum Founder and Executive Chairman Zan Fleming led a historic extended panel discussion on this critical topic that included three current and three former FDA officials, and half a dozen leaders in geroscience and Pharma (see here)...

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Evolving Commercialization Targeting Metabesity Excerpted Transcript

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Targeting Metabesity conferences host not only scientists, clinical trialists, company executives and funders, but also conversations among other leaders from a range of disciplines needed to achieve this aim. The goal is to create interdisciplinary, 'silo-busting' sessions. The speakers come from multiple disciplines, and our panels are formed for lively interactions among experts who may not often communicate. This article is based on a transcript of the two-hour *Evolving Commercialization* session held at the *Targeting Metabesity 2021* conference...

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Fireside Chats with Stephen Hahn, MD and Eric Topol, MD

The Fort Collins Connection

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Two of the Targeting Metabesity 2021 fireside chat panelists were Stephen Hahn, MD, Chief Medical Officer of Flagship Pioneering's Preemptive Medicine and Health Security Initiative and Eric Topol, MD, Founder and Director, Scripps Research Translational Institute. Both, Dr. Hahn and Dr. Topol discussed healthy longevity and provided an introductory platform of knowledge for the rest of the conference. Below are summaries of the key points from each session. Click here to view a recording of Dr. Hahn's fireside chat. Click here to view a recording of Dr. Topol's fireside chat...

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Introduction by Thomas Seoh, JD:

Several years ago, after the sudden loss of a Kinexum member to a freak accident, Zan commissioned a regular feature in our newsletter of personal bios of Kinexers to help fellow Kinexers and clients get to know our consultants on a more personal basis. In this issue, we feature a pair of sportive, musical, altruistic, animal loving friends from Fort Collins: Kate Norton, a regulatory affairs expert with a particularly solid background in CMC, and Ann Donoghue, a regulatory affairs expert both for human and veterinary product development. Read below for how Kate waved regularly to deposed Panamanian dictator Manuel Noriega and helped Kenyan girls stay in school, and how Ann swam the English Channel and the Bosphorus Strait and is an astronomy, ham radio, equestrian and knitting enthusiast...

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Continuation of the Above Articles

A Note from the CEO (cont.)

...Recordings of all sessions can be found HERE. These extended essential summaries in this issue, on regulatory pathways and on commercialization of longevity products, as well as fireside chats with former FDA Commissioner Stephen Hahn and Scripps' Eric Topol, illustrate the insights and provocations to reflection that characterized the full conference.

We also offer a 'two-fer' in our recurring feature introducing the personal side of Kinexers, with profiles of two Fort Collins friends and Kinexers, Kate Norton, who regularly waved to deposed Panamanian dictator Manuel Noriega, and channel swimmer Ann Donaghue.

I want to alert readers to our upcoming Kitalys webinar with Stanford's Michael Snyder, a world leader in integrating multi-omics and Big Data from wearables to bridge from Personalized Medicine to Precision Health, on January 19 (register HERE), and our annual favorite Kinexum webinar, "Wow! Or Yeow?! – FDA Outlook for 2022 and Beyond," with an all-star panel of FDA lawyers and consultants, on January 28 (register HERE).

Finally, I wanted to comment on a couple remarkable webinars I watched during this virtual JP Morgan week featuring late clinical stage and marketed "digital therapeutics" targeting disease-modifying CNS interventions. Cognito Therapeutics is about to start pivotal trials using electrical therapies to slow or stop cognitive decline and loss of brain volume in Alzheimer's. Medrhythms is using sensors, music and software to build evidence-based neurological interventions to measure and improve walking. Akili Interactive is marketing the first FDA-authorized video game to treat ADHD. Neuroelectrics is commercializing skullcaps that measure EEG, amassing clinical applications to diagnose and treat diseases and conditions from epilepsy to neuropathic pain to mood disorders to loss of memory in dementia and executive function in children with ADHD.

These digital therapeutics on the device side appear to be surging ahead of molecular therapeutics on the drug side in multiple ways, including:

- targeting and demonstrating disease modification, which these companies define as making improvements in brain function and structure that persist after cessation of treatment, and that put the disease course on a delayed or reversed trajectory
- generally safer profile, with fewer Adverse Events and especially very few Serious Adverse Events
- an alternative to the patent cliff model, in that more treatment experience leads to a safer and more effective device, due to collection of more data that drive refinements in personalized administration and interpretation of the data
- a more receptive FDA CDRH that may be more free in granting Breakthrough Designations, with a dedicated Digital Health Center of Excellence and emerging guidances e.g. for software and AI
- certain standards of deficit recovery on the device side (e.g., MedRhythm's stabilization of walking for stroke victims, cognitive impairment or brain volume reduction in Alzheimer's) could (if relevant) be cited in discussions about endpoints on the molecular therapeutics side
- the amassing of more and more data and experience could lead to better characterization of earlier or pre-disease states, more naturally opening the way to the possibility of usage for prevention.

Regular readers of *Kinexions* know of Kinexum's and the Kitalys Institute's commitment to targeting metabesity and preventing chronic diseases; digital therapeutics could in some cases serve as a model for our efforts in preventive molecular therapeutics, e.g., in considering risk-benefit standards and relevant endpoints, in seeking some dedicated Center of Excellence or Division for Longevity Therapeutics at FDA and in paving the way for preventive therapies. Food for thought - we live in fascinating times.

- Thomas

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A Note from the Chairman (cont.)

...We have observed—and in some cases been in—the picture of quite amazing scientific discoveries and clinical confirmations of immense value to humankind. They are coming faster and faster. Even the Pandemic has had its silver linings in stimulating scientific discoveries and their translations into marketed vaccines and treatments. Those discoveries did not come out of nowhere, but were built on decades of work in the lab and the clinic. And, the science and technology that has ensued from the COVID realm will not dissipate and instead support a wide diversity of applications across major diseases.

An example of this ascending discovery-development cycle is found in the work of my esteemed friend and co-founder/co-chair of the Metabesity Conference, Dr. Lawrence Steinman of Stanford University. Larry is one of the most prolific life scientists and therapeutic developers whom I know. Larry, both a preeminent immunologist and neurologist, was one of the first to utilize synthetic DNA plasmids as a therapeutic modality. [Plasmids are circular strands of DNA that instructs cells to make RNA, which in turn serve as templates for the cell to make a protein. Presenting the protein to immune cells by this mechanism is more effective than just injecting the protein. The Pfizer and Moderna mRNA vaccines are linear strands, not plasmids, but are manufactured from DNA plasmids.] Larry sought a way to turn off autoimmunity that leads to a variety of diseases, knowing that he needed to trick the immune system in a way that would turn off the attack without impairing normal immunity. He targeted multiple sclerosis and type 1 diabetes with specially designed DNA plasmids, which were a kind of vaccine against the self-antigens that were being attacked. Instead of increasing attack of the self-antigens involved in these diseases, the plasmids were designed to induce tolerance to these antigens, i.e., turn down the attack of the immune system on healthy tissue. Larry demonstrated proof of concept for this approach in both MS and T1D clinical trials. Some DNA vaccines have been approved for animals, and DNA vaccines for treatment of cancer are under development.

For various reasons, DNA vaccines have not gone very far, but in the meantime, along came COVID. A few scientists, having benefited from those lessons learned with DNA vaccines, thought to try mRNA for COVID vaccines—and the rest is history. However, now some attention is being given to DNA vaccines for COVID because DNA is much more stable than RNA. Likewise, some thought is being given to mRNA vaccines for autoimmune disease. So, the inventors of the Moderna and COVID vaccines, to some extent, stood on the shoulders of Larry, and Larry and his colleagues may yet stand on their shoulders to develop new vaccines or treatments for autoimmune disease.

Larry and his Stanford colleague Bill Robinson have had another angle for developing a vaccine for MS by accumulating immunologic evidence that the Epstein Barr virus may be the trigger for the development of that disease. Their work has just been complemented by a just reported epidemiologic study that revealed virtually all the individuals in a large cohort of MS patients have evidence of previous EBV infection, but even more importantly, the few MS patients in this cohort who were initially EBV negative went on to become EBV positive. A MS vaccine based on an EBV antigen could prevent or even treat this condition. It could turn out to be an RNA or DNA vaccine. Larry is on it. Listen to his fascinating radio interview here that starts with the history of this virus.

Larry is also teaming up again with his longstanding collaborator Sir Marc Feldmann, who was responsible for identifying tumor necrosis factor as a primary mediator of joint destruction in rheumatoid arthritis. This discovery opened up the field of anti-TNF monoclonal antibodies, which became the most commercially valuable therapeutic class of all time. Larry himself was right in the thick of that field. Larry and Sir Marc are now repurposing these anti-TNF agents for other indications.

And, so it goes: Scientists build on their own work and the work of others, in long and short cycles that lead as often to surprises as expectations. The one thing that is certain is the uncertainty of where the next breakthrough discovery or product will come—and when it will come. Looking back does remind us to stand on the shoulders of those who have gone before us—and keep going.

To your health,
- Zan

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Clarifying Regulatory Pathways for Longevity Products (cont.)

...The session was:

Evidence 3 | Establishing Clear Pathways for Healthspan Products
How do we get evidence in a timely and efficient way to support use of a product aimed at increasing healthspan? What regulatory pathways and indications are currently available (or are needed) for approval of healthspan products? What are the roles of functional endpoints and biomarkers in supporting development of healthspan indications. What should a phase 3 clinical trial of a healthspan product look like?

Moderator: Alexander Fleming, MD, Founder and Executive Chairman of Kinexum, USA
Gordon Cutler, MD, Formerly Chief, Section on Developmental Endocrinology, NICHD, NIH, and Distinguished Medical Fellow, Eli Lilly & Company, Kinexum Consultant, USA
Mark Espeland, PhD, Professor of Gerontology and Geriatric Medicine and Public Health Sciences at the Wake Forest School of Medicine, USA
David Fox, JD, Partner at Hogan Lovells, USA
Stephen Grossman, JD, President of HPS Group, Formerly Deputy Assistant Secretary for Health, Regulatory and Policy Consultant, USA

Brian Harvey, MD, PhD, Principal Consultant at Brian E Harvey LLC and Entrepreneur in Residence at Yale University, USA
Theresa Kehoe, MD, Director (acting), Division of General Endocrinology, Center for Drug Evaluation and Research, U.S. Food and Drug Administration
Peter Libby, MD, Cardiovascular Specialist at Brigham and Women's Hospital and Mallinckrodt Professor of Medicine at Harvard Medical School, USA
Joan Mannick, MD, Head of Research & Development at Life Biosciences, USA
Line Jee Hartmann Rasmussen, PhD, Senior researcher in the Department of Clinical Research, Copenhagen University Hospital Hvidovre, Denmark and the Department of Psychology & Neuroscience at Duke University, USA
Ed Saltzman, Executive Chairman, Cello Health BioConsulting, USA
Jeffrey Siegel, MD, Office Director, Office of Drug Evaluation Sciences, Center for Drug Evaluation and Research, U.S. Food and Drug Administration
Sue-Jane Wang, PhD, Biomarker Lead/Liaison and Deputy Division Director in the Office of Biostatistics, U.S. Food and Drug Administration

The full 2 hour video recording, including the slides that were shown, can be found on our Kitalys Institute YouTube channel, here. Below are edited excerpts from the far-ranging discussion on matters such as how delaying or alleviating sarcopenia, enhancing immune system resilience and delaying a basket of chronic cardiovascular, stroke and cancer conditions could guide the way for anti-aging indications. This "can't miss" discussion should be of interest to anyone involved in the discovery and development of longevity therapeutics.

EXCERPTED TRANSCRIPT:

Alexander "Zan" Fleming, MD:
Among the questions we are going to address in this session is first of all, how do we get evidence in a timely way? We can't do trials with survival and lifespan as the end point. We have got to come up with more efficient and creative ways to get products to people who need them. Of course, we are not just talking about drugs or devices, but even unregulated products. How do we get the evidence to take a product to highest and best use? Then, what are the regulatory pathways and indications that are currently available or are needed for approval of products that are aimed at increasing health span or healthy longevity? What are the roles of sort of intermediate endpoints, functional endpoints, and biomarkers supporting development of health span indications? And then, what should a Phase 3 trial of a health span product look like?

What are the problems we are trying to solve here? Already approved products for other indications cannot be expected to have enough of an effect size to be detected in a short period of time, particularly in a pre-disease population. And, we have no validated biomarkers to support earlier approval of these products. My first NDA approval when I was at FDA was the first statin and we just took a leap and said, LDL cholesterol was good enough. And that turned out to be right, but not all lipid measures have proved to be good indicators. Even LDL cholesterol itself is not always indicative or reflective of overall cardiovascular benefit. And worse, validation of biomarkers could require positive clinical outcome trials of interventions [that could] take decades or more to complete. We need greater understanding and general agreement of what would be necessary and sufficient to get these regulated products on the market and to have some kind of confirmation of non-regulated products and their value.

We are going to spend the first half on some high level discussions talking about commercial conditions, regulatory law, and whether mechanism makes a difference in this context as to how the product works and how far you need to go to demonstrate the mechanism of a particular product. The second part of our two hours will be devoted to drilling down into these issues, biomarkers, and what I would call stepping stone indications, which might allow us to incrementally get towards a robust health span type indication. We will be bringing Joan Mannick back because she has already, in my opinion, demonstrated proof of concept and a way of taking advantage of a particular mechanism and showing that it can have some benefit or at some level, in her case, the incidence of an infectious disease. Then, we are going to talk about biomarkers that Line Rasmussen has been particularly important in helping to develop [for sarcopenia]. And then we will be getting to a composite endpoint that Mark Espeland and Nir Barzilai and others have helped to develop.

I would first say that we wouldn't expect the term health span or healthy longevity would appear on a drug product label, but an indication could look like this

PreFormin® is indicated for reducing the risk of multiple, chronic age-related conditions including diabetes, cancer, cardiovascular and neurodegenerative diseases, and nonalcoholic steatohepatitic (NASH).

—that is not just for the prevention of one disease, but for multiple diseases. We will have to see that the product has an acceptable benefit to risk relationship. This is in younger people, people who do not yet have the disease.

Ed, why would anybody want to develop a product that has such long odds or such a long road to hope? Let's say we had a product that FDA had approved, who is going to use it? Who is going to pay for it? What would its kind of valuation be? If people are not going to immediately perceive the benefit, there is no good way of knowing whether the product is working.

Ed Saltzman:
Thank you, Zan. The short buzzkill answer, I think, is they won't. At least not now.

I'm amused by the concept of “Preformin.” I think it's provocative. [But] the question I struggle with in this field is — is progress in science and therapeutic innovation in this particular field being hindered to a greater extent than almost in any other field by the lack of clarity around business model, which includes regulation? Then what is the cost of that innovation being crippled? We don't tend to have those conversations in oncology. We do these days tend to have those conversations in metabolic diseases, where these are not the most popular flavors of the moment. And they haven't been flavors of the moment for a decade or more in early venture financing, which is what we know is necessary to spur innovation. So I would just conclude with the fact that we are looking at actually a problem that will cripple the economic growth of the United States and most of the developed world.

So, I think that that is where I would start. We need product. We need a program. Zan, to your specific question, what would one look like? It would look like a product that is safe; that can be used over the long term in relatively healthy people, relatively healthy individuals without an overt disease that is classified. And finally, that may be used in subsets of patients who, regardless of what biomarker we ultimately settle on, it is going to be so critical that we be able to push that field forward because those people are going to be the people that are going to be the first

candidates to take that medicine. A fairly significant portion of statin use are drugs taken by relatively healthy people for a really long time to reduce a risk of a long-term complication. But, when I say relatively healthy people, I don't analogize immediately to diabetes, where we don't have overtly healthy people. So my best guess in answer to your question Zan, is that it would be a product that was indicated for a clearly identifiable, possibly genotypic, group of patients who would be at risk of the development of chronic disease.

Alexander "Zan" Fleming, MD:
Speaking to biology, there is often a question about how important is it to understand mechanism for regulatory approval. We know it is important scientifically, but there is a practical question about just what is necessary and sufficient for various purposes, regulatory being at the top of the list. So, I'm going to bring in two of our FDA experts here, Theresa Kehoe and then we have Jeff Siegel, who by the way brings industry experience and really has in his brief responsibility for validating various end points including biomarkers. Along with my colleague, Peter Libby from Harvard, who is a preeminent cardiologist, but his work ranges from the very basic [science] to large clinical trials. How much do we need to know the mechanism about the intervention, particularly a drug or a pharmaceutical intervention?

Theresa Kehoe, MD:
I'm going to start with an example. My division has some experience with healthspan products, obviously, because we regulate both the osteoporosis and bone loss world, as well as the muscle loss and the sarcopenia. Both of these, you reach your peak in your early thirties, and then it's downhill from there. And I think what we have learned from osteoporosis is if you go back and look at the eighties and early nineties was a biomarker was accepted and that was bone mineral density. But then, you get into a situation, specifically fluoride, where the bone mineral density was huge, going up 30% in some patients, but it did not improve the fracture risk; patients were fracturing anyway. So, we learned from that, there are underlying mechanisms that we need to know about because what was happening with both fluoride and also one of the first bisphosphonates, was that it was affecting the underlying bone mineralization. So, we do have to have some understanding of the underlying mechanism and how it translates for all of the different areas that are being pursued. But, you also need to think about dose ranging because perhaps for each of those different areas, there will be a different dose of the product to be able to do any good. So, I think that's where the mechanism—we at least need to have knowledge enough to be able to look in the right places to make sure that the safety is there.

Jeffrey Siegel, MD:
Just to reiterate, I'm the Office Director for the Office of Drug Evaluation Sciences, which is responsible for qualifying clinical outcome measures and biomarkers across therapeutic areas. So, these discussions are very relevant for the work that we do. In terms of mechanism, I have worked at FDA for a long time. I was also in industry for 11 years, as you mentioned, Zan. And from my experience in drug development, understanding the mechanism is really critical.

There was a paper talking about the hallmarks of aging, and they ranged from mitochondrial dysfunction to telomere length and so on. I think that the mechanism that a drug targets may determine which indication is most likely to benefit from modifying that pathway. Another important consideration is the drugs that are not targeted at a mechanism can work, but I think they are much less likely to work because designing a drug to target a particular mechanism or particular pathway allows you to have much more targeted effect. And, it's much more likely that you will be able to hit the target and have an impact on the disease question. But beyond that, if

you know the mechanism, then you understand what the target of the drug is and you can devise pharmacodynamic markers to monitor how well the drug is impacting the pathway in question. And if you don't have good pharmacodynamic markers, you can't do adequate dose ranging. You may limit your drug based on toxicity and not based on how well it inhibits the pathway in question, and that's not a good way to do drug development. And then finally, an important way that mechanism matters is that there are a lot of different types of biomarkers—prognostic biomarkers, pharmacodynamic biomarkers—but ultimately, I think there is a lot of interest in surrogate endpoint biomarkers. To develop a good surrogate biomarker, you really need to know that your drug is on the causal pathway to the condition—the deleterious condition in question, the disease in question. Otherwise, you can run into problems with off target toxicities or situations where the biomarker correlates with the clinical outcome, but isn't on the causal pathway and that can fool you in drug development and prevent you from developing a true surrogate biomarker.

Peter Libby, MD:
As I'm wearing my scientific hat, obviously, I'm interested in mechanism. It's what I spend a lot of my time thinking about doing, but in fact, biological plausibility is the last refuge of scoundrels. I think the gold standard has been the randomized, controlled clinical trial. And what I'm intrigued by is that we are going to be talking today about therapeutics that may not fit that mold. And I want to learn from you guys about how we are going to move that bar forward. But, the thing that we have learned through the decades is humility about mechanisms. We are usually wrong about mechanism. The statin example, how are statins working? Well, by blocking HMG COA reductase, except they also block the prenylation of small G proteins, Ras….they induce some transcription factors such as KLF2, Krüppel-like Factor 2. How much of the benefit is due to things that are totally extraneous from HMG-CoA reductase. So colchicine, another case and point, how does colchicine work? We don't really know. I think probably the … inflammasome inhibitor is at least partly wrong. We have remarkable effects on cardiovascular outcomes with the SGLT2 inhibitors. How has that working guys? Does anyone know? So, could that be predicted from what we know about the renal tubular functions? I think what I've learned in my career is to be incredibly humble about mechanism. Sure, we are going to hang our hat on it. We tell stories about it and we give wonderful talks with beautiful polychrome slides. But in fact, we have to acknowledge the great distinction between our castles in Spain and the reality.

Alexander “Zan” Fleming, MD:
Peter, I love that….I now want to really change gears and go to colleagues who teach me about the law, the regulations, the policies that pertain to therapeutic development. That includes David Fox, who was at FDA as a counsel, and is now a leading partner in the pharmaceutical and related practice at Hogan Lovells. And then, Steven Grossman, who was actually a Deputy Assistant Secretary of Health. You were never actually at FDA, you were just sort of over it; and you were on a Senate committee; and you have a lot of relevant experience about how regulations get written, how the sausage is made. So, you two are my go-to authorities on this kind of thing. Let's talk a bit about what are some of the challenges, and Steven you have put this down on paper, you see some challenges. I'd like to see maybe a little bit of give and take here with David on that.

Steven Grossman, JD:
Well, thank you. I would add that while what I wrote was meant to be provocative, I decided I believed it as well. I guess my premise is that health span products don't fit. Somebody in the chat room was talking about breaking down silos and that’s only going to work if you destroy the whole property and start from the beginning. They need their law, their own standards; they need their

own approval process; and they need to envision a post-approval marketplace. That's different. That's not what we have today. I think that it's going to be difficult to start from a blank page. It just defies all of us who have spent years and years and years regulating biological products to think we don't have anything, the cupboard is bare. But, I'd argue it is.

The obvious point, which I know other people are going to raise today, is the FD&C Act does not set up a mechanism to guide the approval of drugs that do not provide therapy for a disease. It is not just something that sits up there; it's the very DNA of our drug approval process. And if you look at well, RX is two well-controlled clinical trials. Well, that's not going to be easy. OTC works off of a monograph system; dietary supplements are historical or proven grass, plus no function or structured play that's attractive. I actually think that one of the possibilities is the animal rule model, where the entry to the new standards is going to be showing in a definitive way that you have safety and that there's a plausible case for efficacy based on animal models. That's also, I mean, it works for anthrax treatments. Does it work for stuff you are going to give to tens of thousands or hundreds of thousands of people? I think there is also another thing that is not so obvious, that is really important, which is the RX model is aligned individual health. What we're talking about, except for vaccines, drugs and biologics are not thought of as being evaluated for addressing population health. But, when we talk about what the subcategory of people is who are going to benefit from statins for life, it's much closer to population health than it is to individual health. So the conclusion from all of this, for me, is if you forcibly retrofit health span products back into the existing drug approval process, it is a prelude to living in a debt, a hell. You thought it was messy. You thought that nobody really understands what FDA did. Start to chew on these products and you will find that was just a little storm, and we got tornadoes coming. Anyway, David?

David Fox, JD:
I think that bold vision of coming up with a dedicated regulatory system, specific to these sort of preventive, preemptive medications over the long haul is where we need to head, but the question is what can we do now? Because we all know that a legislative overhaul creating a whole new category of products is a multi-year undertaking, if not a decade long undertaking, and in today's politics who can predict. So, we have to look at what we have right now and just to get us to the basics, Food Drug and Cosmetic Act, the law defines a drug in a way that goes beyond just treatment cure or mitigation of disease. It expressly includes the prevention of disease. As Theresa pointed out, we are not unfamiliar with prevention claims, osteoporosis is probably one of the best examples for treatment or prevention of disease. But, beyond that, it is fairly slim pickings. We have, however you want to add it up, about 5,000 NDA approved drugs and only about 500, 1 in 10, include a prevention claim. And, most of those are prevention of infection, seizure prevention, prevention of migraine/headaches, prevention of recurrence of a disease state, or prevention of harm from a side effect or from a procedure. So, even the overwhelming bulk of our prevention claims, which themselves are relatively few, about 1 in 10, are all associated with some sort of an acute occurrence. So it is as Steve said, a bare cupboard.

But, that being said, the language, the legal basis for FDA to consider prevention is there. And I think, with conferences like this, Zan with your effort and the collective effort, I think we need to really figure out an advocacy strategy for going back to FDA and opening the door to prevention. The law is there, it's more of a behavioral science question, or as much of behavioral science question, Malcolm Gladwell question, as it is a medical David Sinclair, Zan Fleming question. So, it's the behavioral science piece about how FDA is thinking about disease that needs to change. And, there are tools. So, we have all heard about patient voice, and we know that the patients and

patient advocacy groups that are the most effective, are the ones who are most acutely affected by the disease. That's perfectly understandable, but I think we really need to get patient advocates to start working on the prevention piece. And, we have seen over time how organized patient advocacy can really move mountains. I think that is one tool that is available and can be brought to bear. Second, is the biomarker qualification system. It's cumbersome. It's a public process largely and so, you are doing a public service and it has that issue associated with, it's not a proprietary process, but it is there. I think the door is open, particularly for academia to use it, in our case. And, I think also using it tactically to start the conversation with FDA in a concrete way outside of the four corners of a clinical development program could be an effective way. Again, if we ever want to get a legislative solution, I think showing our failures as much as our successes will be very helpful. Third, there actually is a model in some ways for what we want, and that's health claims for foods, which is more of a sort of consensus, substantial, scientific evidence standard than it is an adequate and well controlled clinical study standard. I think exploring the types of compounds we might be able to push through on the health claim side is another kind of avenue to explore. Again, as much as it may result in rejection, the rejection may also illustrate the problem. Fourth, if you want to get more clever about it is the issue which we don't pay as much attention to, which is safety. And we all expect that tolerance for risk will be extremely low in evaluating compounds or interventions for administration to a largely healthy population. I think the real question there is this question, then it is the question we always come back to, is our population inherently healthy or are we all necessarily trending toward disease? That's the question that I think, as a lawyer the one that's posed to me so often, is aging a disease? Can FDA be encouraged to define aging within the scope of disease?

Now, FDA has never defined disease in the drug area. It has outside of the drug area in the food area, and there's fairly good language that is consistent with the concept of your overall status, your health status, and can be aligned with aging as a disease. So, we asked that question over and over again. I don't have a good answer to it. I do know if we keep asking it, it will lead to our own disease, state of insanity. I think that we at these conferences so aptly put it about the inevitable disease state that we are heading to as a population. Put age aging aside, the biological evidence is so compelling that I think that within the existing paradigm that constellation of age-related diseases is so powerful that we don't need to get caught up in that sort of semantic argument.

So, as I said, I think there is room, a lot of room, to really try to gauge FDA on filling out what is already in the statute, which is Congress's direction from a long time ago, that on equal footing drugs are intended to prevent disease, and patients have a stake in that. We have a bio-marker system that can penetrate the science on it and bring those together. I think, without a legislative change, we can start to close the gap. And then last, I think in the ideal, working with what FDA can actually do now with the social structure, I think we do need a dedicated division or discipline within the agency, not probably at the level yet of a Center for Excellence, but I think we need a separate group of people to think about it outside of the people who think about the acute treatment of diseases. And I think that would really elevate the issue.

Alexander “Zan” Fleming, MD:
We could spend a lot more time just on this very topic, but I would like to bring in some other folks to talk about evidence, in this case clinical evidence, because that ultimately is what it is going to take. We have a lot of animal model data of interventions, which improve lifespan. I would hold up though, Matt Kaeberlein’s rapamycin dog study, which I would say if he is able to show a benefit, survival benefit in dogs, we ought to be looking at that as at least supportive evidence that the product is working. Survival generally trumps everything. But, if you see that in

a species like dogs, you might expect that to hold in humans, but let's stick with clinical evidence for now.

Let's start with, what kind of clinical evidence do we need to see? But, let's start with Brian, a few words about the very long pathway to get a product approved for the prevention of a silent disease. You still start with people with the disease, but they are asymptomatic and they have to be treated for a long period of time to be able to see that benefit.

Brian Harvey, MD, PhD:
I was shaking my head in agreement as Steven was describing the need for a new paradigm. Back when I was in medical training in the 1980s, some of my attendings were part of the Harvard physician aspirin study, and that of course, now was 30 years ago. Under the Food Drug and Cosmetic Act, here we are all these years later, and FDA is still against primary prevention. So, aspirin is a pretty darn safe product. And yet, Bob Temple and others don't think it's yet met the bar of primary prevention and only secondary prevention....that sort of is what we are up against.

In the NASH field, many patients are patients who have had poorly controlled diabetes, hyperlipidemia for 20 years, who then go on to find that they have elevated liver enzymes and get a scan. They find their liver is either full of fat or inflamed or cirrhotic. There is wonderful potential to intervene long before NASH and NASH treatments have been a real challenge every day. You can read in the press, the latest failure in the NASH space. I think part of that is not only because we still don't understand the progression, how many patients go on from a fatty liver to end stage liver disease and how many of those patients actually die of their liver disease? And of course, the paradigm, the prime directive of the FDA accelerated approval is, how well does that surrogate or intermediate clinical endpoint actually predict clinical benefit? The problem is if over half the NASH patients die of cardiovascular disease, are we really going to see a benefit of a reduction of one stage and fibrosis score from a liver biopsy, day zero versus 18 months later? And yet, industry and others who were backing the development, are so focused on trying to minimize the amount of time it takes to get the product approved that they are sort of missing the point that the underlying pathophysiology, which is only partly known, isn't going to change. If it took 20 years to get the patient to that point, you're not going to change course in 18 months. There is a huge potential economic and public health potential for treating these patients. But, it's not going to be a quick fix. We saw a year and a half or so ago that Intercept, who appeared to every step of the way follow FDA's guidance on how to develop a NASH drug, then submit their application and they got a complete response letter. The world has sort of been thrown into disarray because FDA hepatology division has not yet been able to come up with an alternative paradigm. They are saying that the 2018 and the 2019 guidances are still in effect, and yet we have this complete response letter hanging out there. And of course, an accelerated approval only gets you so far. If the outcome trial at the end of the process does not confirm benefit, FDA does have that right to withdraw the accelerated approval. In the oncology space, accelerated approval has been under attack. And of course, in the Alzheimer's space, their Congress has been up in arms over the Biogen approval, and that has a chilling effect on FDA staff.

So, I think we need to change the Food Drug and Cosmetic Act. I think Congress needs to understand that yes, they have oversight responsibilities, but I don't really want our friends on the House and the Senate side to be involved in the approval and review process. On the other hand, maybe the model of the Framingham heart study, where now we are into the third generation of patients trying to use that model, or extend that model when it comes to lifespan, health and things like that, might be the way to go. Things that cut across various sponsors. I think that is the

way to generate the data and at least give us the foundation for some of these treatments that we have been hearing about this morning, and we will hear over the next couple of days.

Alexander “Zan” Fleming, MD:
Let's go to Gordon Cutler, who is a veteran drug developer - you have been looking to improve outcomes in people ranging from post-surgical stress to sarcopenia of various strife.

Gordon Cutler, MD:
I want to respond first to some of the thoughts of the panelists, and just to say that I agree with Brian and David and Steven that ultimately a change in the law would make everyone's life a lot easier and it's arduous, but I think sometimes the big picture gets lost if you try to finagle your way through what's existing. I don't disagree with David that we have to deal with what we have got now. I don't see from my simple minded view, why it would be so hard to say, as we know so much now about the mechanisms of aging, that the role of FDA would include evaluating safe and effective methods to inhibit or delay the mechanisms of aging in order to increase healthy life span and delay cognitive decline, mobility decline, ADL, disability, and other diseases of aging. I guarantee you that for a society that's full of aging people, as Brian says with, for example, Alzheimer's and all of these other areas, to me, this would seem to be make it a lot easier and would probably unleash a tsunami of development.

Now, it will have huge complexities of just how do you define life healthy lifespan. I think once you have Alzheimer's, you don't have it [healthy lifespan]. I also agree with your suggestion, as you hinted at it, the issue of surgical recovery, hip fracture recovery for example typically occurs within about six months. So, it presents something that if you had a way to improve, it could be seen relatively rapidly. It is a disease where universally there is impressive muscle loss in both legs while people are in pain and healing, amazing amounts of muscle like what happens when you send people into space and there is no gravity, they lose muscle. The problem has been so far that there has not been a powerful enough agent and actually so far because it's again a new pathway, so like every new pathway, there isn't an agreed approach to doing it. I thought working with you and others that we were pretty close when we suggested walking speed, where there is a huge amount of evidence that it correlates with future ADL disability, hospitalization, nursing home admission, and survival. Walking speed combined with a patient reported outcome measure, if you could improve both walking speed in the patients saying, “we didn't need a cane; we didn't need a wheelchair; we didn't need somebody holding their arm” would be valid. Unfortunately, with the FDA Director or the Division that we were involved with, that wasn't enough. And it may be that there wasn't the requisite formal approval of this patient reported outcome measure by all of the steps for validation that are needed. It may be that pushing harder on this would have worked.

One other quick thing just came to mind. When you talk about settings the, the patient who's already had a fracture can be done with far fewer patients than the fracture prevention in somebody who's osteoporotic, but never had one. Similarly, it'll be much easier to demonstrate a true survival effect in centenarians, for example, than it will be in younger people. So, I'm not convinced if you really had something that worked powerfully on an important mechanism—mitochondria, metabolic—I have a 97 year old neighbor who brings us food from his garden every year, drives his tractor around, I think he's healthier than I am, and I'm sure he'd love an approach that would help him live and remain healthy longer.

Alexander “Zan” Fleming, MD:

Theresa, sarcopenia indications would be in your division. You've heard some comments in general about FDA authority and discretion, what are your thoughts here?

Theresa Kehoe, MD:
Well, I think with sarcopenia, it's not quite as advanced in the drug regulation pathway. We also deal with cancer cachexia, which is long, and it's the same type of issues that sarcopenia has. One of the largest issues that we have at this time when it comes to drugs trying to be developed for treatment, not necessarily for prevention, is really defining the population to be treated. Right now there are, I think, as many as five different definitions of sarcopenia out there. There is not even a consensus of the definition of the disease. Obviously, we are not the experts at FDA; we are the regulatory experts and can help in the drug development, but we are not the experts in putting the definition out there. So, I think it's really important to have the consensus in the scientific community. Obviously that happened within the osteoporosis world. I'm going to bring in osteoporosis again, because as has been mentioned, prevention is an indication that was given to many of the early drugs for osteoporosis, for the treatment and prevention of the disease. Unfortunately, the osteoporosis prevention indication is a cautionary tale because then after we had patients in their fifties on these drugs who started snapping their femurs; and then, you had these very rare, but very serious side effects that became notable in the post-marketing setting with the osteonecrosis of the jaw and the atypical femoral fractures. So now, what you are left with is nobody wants to touch these drugs that clearly work to treat the disease and prevent the fractures. I think it's a caution because I think perhaps it was too much concentration on prevention and now you can't even get patients who really need the products for treatment to take them.

Jeffrey Siegel, MD:
I guess the main area that I want to contribute in here is developing and qualifying clinical outcome assessments, like functional end points. The key thing here is to understand what matters to the patient most. So, understanding of patient population that you are talking about, what the impact of the disease is, and how it impacts the patient. Then, you can formulate your concept of interest and figure out how your functional measure will assess that concept of interest. Then, for a functional measure, which may be a digital health technology, you need to make sure that it has validity, so that it is reliable, accurate, that it measures what it is supposed to measure; and then, clinical validity that it measures accurately the concept of interest that you have in mind by correlation and other methods. This is a long road to hoe and it is complicated. I'm sorry that the process is as complicated as it is and cumbersome. I recognize that. Since I started in my current position in February, it's been a key goal of mine to understand what the stumbling blocks are in the way of qualifying more clinical outcome assessment measures, more biomarkers, and I've identified some. If there are others that people would like to share with me, I would love to hear about them because I do think that we need to make sure that we make these tools available for drug developers to bring important medicines to patients. I know that will help your efforts in developing medicines that can help increase healthy lifespan, but also treating these diseases that are increased in incidents with aging.

So, someone mentioned that the qualification process was intended to be an open public process, and it's absolutely true. There are provisions for transparency. So, the performance of the tool needs to be put publicly on the website afterwards, but that doesn't always mean that every aspect of it is made public. There are approved, qualified clinical outcome assessments where there is an aspect of the algorithm, which is not public. But, the performance of it is and the general concept of the clinical outcome assessment or biomarker is. I think that it would be a shame to exclude

industry from developing helpful biomarkers and helpful clinical outcome assessments. So long as we can work within the intent of the law for transparency, I think that industry has a lot of resources that can really help with things that could benefit everyone.

Alexander "Zan" Fleming, MD:
Thank you so much. Sue Jane Wang, you have been involved, you have had responsibility for the statistical side of biomarker qualification, and we will be coming back to you, but do you have any reactions here?

Sue-Jane Wang, PhD:
Yes, so perhaps just briefly. Thus far, we had qualified three clinical biomarkers. One is a diagnostic biomarker. The other two are prognostic enrichment biomarkers. The goal there with the qualification was that once it's been qualified, industry, where are they do drug development, could pick it up and then use them within their own particular drug development for the qualified context of use. I often use total kidney volume as an example because in this case, the statistics office contributed a lot to facilitate the eventual qualification, which is a collaborative effort. In this qualification, I had led the team to do the work. We did allow more than what the requester had done. And, we also tried to illustrate the evidence for qualifying the biomarker as a prognostic biomarker for clinical trial enrichment. Eventually, the total kidney volume as a prognostic enrichment biomarker after it's qualified. We actually told the requester that they probably should consider the qualification as a surrogate endpoint, for example, or reasonably likely surrogate end point, that they would need to go through yet another round of qualification, because now the context of use has been changed. With that in my mind, I have been waiting for such a submission to occur, but interestingly, through the individual drug development, multiple clinical trials were done. Not only did they look at the total kidney volume biomarker as a prognostic biomarker, not necessarily enriched in the clinical trial, but was able to find the benefit of the total kidney volume as a outcome measure. But, that benefit without the actual clinical eventual outcome is unclear. The division now this is actually looking at the total kidney volume biomarker as a reasonably likely surrogate endpoint. So, it didn't go through the qualification space, but it did allow the advancement of the drug development through that initial qualification and it to be able to move one step ahead. I thought that is a utility for that intermediate clinical evidence, not a true clinical evidence as yet.

Peter Libby, MD:
I'd like to make a clinical observation. Most of the males on this panel have gray hair. I would like to actually enlarge the conversation to encompass the other side of the spectrum. Let me explain why, because as a preventive cardiologist, I'm struggling with how we deploy preventive therapies, not to the old, but to the young. We now are in possession of very potent and validated polygenic risk scores, so that I can tell a neonate, probably tell a fetus, what their cardiovascular future is going to be like. Now, the way that I put this, if any of you reviewing my grants, please read this beautiful poetic part, where I say that the polygenic, which you inherit from mom or dad, is the sketch on the canvas of cardiovascular risk and that how you make the full portrait depends on your behaviors and your exposures. So, we have in hand today tools where we can tell that a kid has a higher cardiovascular risk. Now, obviously we are going to do everything we can with lifestyle. And we all know the obstacles and barriers to effecting lifestyle change. But, in terms of pharmaceuticals or therapeutic approaches, how can we show? How are we going to show that if you treat an eight year old that you are going to be improving outcomes? It's the same problem, but on the other end of the spectrum, and I don't want you guys to ignore that because it's a huge opportunity for prevention and for successful aging if we start really in youth. So, it seems to me it

is the same generic problem, but I just want to put that on the table to expand the conversation.

Alexander "Zan" Fleming, MD:
We could spend another few hours on this particular topic, but let's start to drill down into various specific approaches that could be used. You have provided a great segue to Line Rasmussen. We are delighted to have you give this presentation on two different approaches that you have been very involved in, gait speed and chronic inflammatory markers as biomarkers.

Line Rasmussen, PhD:
I'm very excited to be able to share some of our findings. Most of which comes from the Dunedin study, which I've been working on with the Moffitt-Caspi lab at Duke University. I'll just give a super brief overview of some of our findings on gait speed and systemic chronic inflammation. The point of this is to show you that there is variation in these biomarkers already among people in their forties and how this variation is biologically meaningful so that it can distinguish people who are faster aging from those slower aging.

The data we use comes from the Dunedin Longitudinal Study, which follows a population representative birth cohort of 1000 individuals, who were all born in the city of Dunedin in New Zealand in 1972-73. These participants have then been followed for their entire lives all the way up to the latest assessment in 2019, when all the participants were 45 years old. This study is very famous for its very comprehensive data collections and also for its really impressive retention rates. For example, at the last assessment at age 45, 94% of all the participants who were still alive took part in the assessment. So, at age 45, gait speed was measured. And then, I'll also share some findings on a new inflammatory biomarker that we have investigated, which is called suPAR. We have looked at that at age 38 and 45.

Since this is still a very young cohort, we don't have a lot of data on traditional aging outcomes yet. For example, disease development or mortality, but there has been collected very rich data on other validated aging outcomes. For example, MRI scans of the participants' brains, full cognitive assessments, different measures of physical function, and then, this measure of facial aging, where we had independent raters assess how old they thought each participant's face looked based on standardized photographs. This picture summarizes the facial age results by showing composite image averages of the 10 slowest aging, average aging, and fastest aging study members. It is pretty striking to see how big a difference there is because all of these people were actually 45 years old. In addition, we used a quantitative measure of biological pace of aging, which assesses the functional decline in 19 biomarkers across multiple different organ systems. This was assessed between age 26 and 45.

So, gait speed is a very interesting measure to use, and we have heard about it several times today, but it is a good and very quick and easy measure of functional decline. The reason is that a simple thing as how fast a person walks depends on the function and interplay of many different organ systems at the same time. You need your nervous system, your vision, hearts and lungs, bone and muscles, and so on. All of this has to work in order to be able to walk. Therefore, gait speed captures the underlying health of a person and it is the thought to be a good measure of the functional capacity of a person. It is a common measure in geriatric settings, and it's mainly been studied in older adults and been found to be associated with the accelerated aging and a whole range of negative health outcomes.

But, in the Dunedin study, we measured gait speed on a six meter electronic walkway. The beauty

of the gait speed test is actually that you can measure it on any flat surface, just using a stopwatch. So, that makes it a really easy and convenient measure to implement in different clinical and research settings. We measured gait speed in three different ways. The usual gait speed, which is just the normal walking speed of a person; the dual task gait speed, which is where a person is asked to walk at their normal pace while reciting alternate letters of the alphabet out loud, and that is actually a lot harder than it sounds; and then, the maximum gait speed, which is just to go as fast as safely possible without running. We found that gait speed was normally distributed for each condition. And, we basically found the same associations with our aging outcomes for each of the three walk conditions, although with larger effect sizes for the two challenge walks, especially for the maximum gait speed, which could suggest that this might be a more sensitive measure among people at midlife.

We found that gait speed at age 45 did already reflect accelerated aging. Here, we have the participants divided according to gait speed quintiles, with the slowest walkers and the fastest walkers. The 20% slowest walkers had an average gait speed of 1.2 meters per second, which is similar to the average walking speed of older adults in their seventies. The fastest walkers had an average gait speed of 1.8 meters per second. So, there was quite a big difference even though they were only 45 years at the time of the test. Those who were slowest walkers had a higher pace of aging across the 19 biomarker measure. According to this index, those who were the slowest walkers had been aging 5 years faster than the fastest walkers in the study since age 26. In addition, the slowest walkers were also rated to have older looking faces. We also found that gait speed at age 45 was associated with cognitive function. So, those who had slow gait speed had a lower cognitive function and they also exhibited a greater cognitive decline. We found that slow gait speed was associated with multiple signs of structural age-related changes of the brain, including brain atrophy and the burden of white matter hyperintensities, which are these small lesions in the brain that are associated with cognitive decline and risk of dementia. That was also a pretty striking finding at this early age. So, in general, it seems like gait speed at age 45 is already capturing aging differences and differences in functional capacity, making gait speed a potentially good measure in clinical trials as an intermediate endpoint.

Another measure we have discussed today is the systemic chronic low grade inflammation, which is considered a hallmark of aging and is known as a major driver of many different chronic diseases. There is a long list of risk factors for systemic chronic inflammation, including unhealthy lifestyle, obesity, and other effects like social isolation and psychosocial stressors. This long list of risk factors also suggests that there are many different potential intervention targets to reduce systemic chronic inflammation. But, as this Nature Medicine review pointed out, there are still no standard biomarkers for assessing the underlying level of systemic chronic inflammation and it is typically measured by combining various biomarkers of acute inflammation instead. As with many of those traditional biomarkers, for example CRP or various cytokines, they are often also sensitive to acute infections and acute change. It is more difficult to interpret these with regards to systemic chronic inflammation. But, in the Dunedin study, we have been investigating a newer biomarker of inflammation called suPAR, which could maybe be a more robust measure of systemic chronic inflammation.

We measured suPAR at age 45 and we found that high suPAR, much like a slow gait speed, was associated with multiple signs of accelerated aging. We found that those with highest suPAR had a higher pace of aging across the 19 biomarker measure. They had older looking faces and they had signs of age-related changes in the brain. In addition, those with high suPAR levels have lower cognitive function and a greater cognitive decline compared to participants that had low suPAR

levels. suPAR increases with age, and we and others have shown that unhealthy lifestyles are associated with elevated suPAR levels. Smoking, in particular, is a major risk factor for elevated suPAR. Current smokers have high suPAR levels while never smokers have normal suPAR levels, but those who quit smoking decrease their suPAR levels to a level similar to that of never smokers. We have also shown in the Dunedin study and also in the independent E-Risk cohort from the UK, that suPAR is associated with various types of stress across the lifespan. For example, adverse childhood experiences (ACEs) or as shown here, with the number of adult stressful life events. Interestingly, we found that neither CRP nor IL-6, which are two classic inflammatory measures, were consistently associated with the ACE score or adult stressful life events in these studies.

The findings from our studies add to a growing body of evidence that suggested suPAR could maybe be a potential biomarker of systemic chronic inflammation. The blood suPAR level can be easily measured just with a standard ELISA. suPAR lies between early risk factors and more distal outcomes in that it is associated with a wide range of the same risk factors as a systemic chronic inflammation and age-related disease in general, and it is associated with a wide range of diseases, including many chronic age-related diseases. It is associated in the way that it is both predictive of —and elevated by—different diseases. In contrast to many different or more traditional inflammatory biomarkers, it seems to be more stable and less associated with short term acute influences. For example, it is not dramatically affected by small acute infections, but it is associated with levels of other inflammatory biomarkers and with immune activation. The suPAR level can be altered by various anti-inflammatory interventions or lifestyle changes, such as quitting smoking or by treatment of disease, making this a modifiable risk factor.

Just to sum up very briefly, we found that both gait speed and suPAR are two measures that are associated with aging already in a population representative cohort at midlife. Both of these are associated with the 19 biomarker pace of aging. There might be interesting targets for intervention among those 19 biomarkers. And also, suPAR for example, could be a potential endpoint, which could be used in an intervention study as an effect measure to test whether various interventions on health will result in a decreasing suPAR level without having to wait for many years for traditional outcomes to develop since it's strongly associated with disease development and also with mortality. That was it for me. Thank you very much.

Alexander “Zan” Fleming, MD:
Thank you, Line. That was right on the mark. Jeff, we have an example of a biomarker candidate and a functional endpoint. You might parse the difference, but of course, I'll put this to you. And then, I would ask Theresa to comment and we will be talking about sarcopenia shortly, with Gordon Cutler maybe chiming in. There is a difference between something that is correlated with a benefit and may turn out to be with an intervention improved. But, when you have something like gait speed, there is some degree of face validity there. As you know, FDA has approved drugs on the basis of a similar functional endpoint, six minute walk, but the proposition here is why not gait speed? Gait speed would be much more easy to implement in a large clinical trial setting. Why is it not? We will ask Theresa to be thinking about this. Why would it not be both necessary and sufficient for approving a sarcopenia therapy, if you could show an improvement in in gait speed? So Jeff, what are your thoughts?

Jeffrey Siegel, MD:
When we think about qualifying clinical outcomes assessments and biomarkers, we think about the concept of interest and about the context of use. So, the concept of interest would be some aspect of the disease in question, if that is sarcopenia, maybe it would be physical function, or

something like that. And, the context of use would be how you are going to use the biomarker. For the concept of interest, you would want to do assessment of patients with the condition, find out what matters to them about their disease and what would be a meaningful benefit of a treatment—if it's a prevention of worsening in physical function or improvement in physical function—and how much of a change would be important to the patient to be considered clinically meaningful. That would be that aspect. Then, the context of use would be how are you going to use it? You might use it as a biodynamic endpoint to show that treatment impacts it in the video target. You might want to look at it as a prognostic endpoint, selecting patients most likely to benefit a treatment, or you might want to look at it as a surrogate endpoint, actually corresponding, correlating very closely with the benefit that you expect to see so that you can predict with a high degree of certainty that an impact on the surrogate will correspond to a long-term benefit. I'll have to defer to Theresa to talk in more detail about what would be meaningful for patients with sarcopenia.

But, I want to go back to something that Sue Jane said and she stole my thunder by saying what I think is a really, really important point, which is the FDA listens to data. We have no intention to be obstructionist in any way. Our goal is to help public health, like all of us want to improve public health. But, we just want to make sure that a drug that we approve really does improve the lives of patients and that any adverse effects that it has don't counterbalance the benefits. We listen to data. If you bring us data that the treatment in question has a particular benefit, we will pay attention to that. Similarly, for biomarkers, if you try to go too quickly to a surrogate endpoint, amassing the amount of data to approve a drug based on a surrogate endpoint, it's just daunting to even imagine how you would go about amassing all that data. But, if you do it step by step, it can happen in a very simple and organic way. You can start with the formal pharmacodynamic endpoint and demonstrate that it does measure the ability of the drug to hit its target. You can look at it as a prognostic endpoint, so that levels of the biomarker, like gait speed, correlate with outcomes down the line that would provide evidence that it is a prognostic biomarker. Then, you put it into randomized clinical trials and show that the change in the biomarker correlates very closely with the clinical outcome assessments. Then, you're in a very good position to argue that it can be used as a surrogate endpoint. So, doing it step by step, by baby steps, is probably a more realistic way to get to the goal that you want rather than going right away to a surrogate.

Alexander “Zan” Fleming, MD:
That is very helpful again, Jeff. Let’s, as you suggested, go over to Theresa and take the example of sarcopenia and Gordon Cutler is coming to you to propose gait speed alone as a primary efficacy endpoint with a stated effect size that is viewed or is actually shown to be clinically meaningful. What is wrong with that?

Theresa Kehoe, MD:
Well, I think we need to see the data, as Jeff has already said. Then, I think right now, one of the struggles that we have is in the sarcopenia realm, how much do we need muscle mass measurements? Do we need to see that the intervention is increasing the muscle mass, as well as increasing the muscle strength and muscle function? This is where the various definitions of sarcopenia can affect it. It depends on who you talk to. There is not a consensus, and that is one of the issues and one of the struggles that we have in the field. I know there has been a lot of looking at not only gait speed, but also hand grip strength and the correlates of hand grip strength. When you look at the FNIH project, it didn't correlate very well; depending on how you looked at the data, the correlates were different. So, I think we do need to see the data that gait speed would be sufficient. We would likely recommend that you use gait speed, as well as some clinical outcomes

assessments that are being developed. They are currently under development. So, you are not necessarily starting out with the gait. And then, the question becomes whether we would need to see the muscle mass increase as well.

Alexander "Zan" Fleming, MD:
Nir Barzilai just made the important point that what we really need to do is to prevent sarcopenia, not to try to reverse it because reversing that it has been dauntingly difficult. But, here is the point, if we can show a difference in the decline of muscle mass and function, why would that not be a valid way of approving the therapy for healthy longevity?

Theresa Kehoe, MD:
I think you may be able to. It depends on the context; it depends on the patient population that you have. And, the other question that arises from this is: in a lot of very chronic diseases, you are using the pharmacologic intervention as an adjunct to other things, would you—and we have not required it, but I think it is something to be thought of—would you require the intervention to be an adjunct to resistive exercise? So, that both groups get resistive exercise, is that actually sufficient? And then, would you add something in addition to that? I think this is for us a work in progress, as I said, there is not much activity from our standpoint, from the sarcopenia realm, as yet, the field is obviously advancing very quickly. We are trying to keep apprised of everything that is going on for that. We have more experience in the cancer cachexia realm, which is really a different disease state, but similar.

Alexander "Zan" Fleming, MD:
What a great discussion on biomarkers and intermediate end points. Jeff has described an open door policy for FDA and Theresa has reflected an open mind on coming again with data when we have a product that works. I would like to now shift gears and go to Joan Mannick, who has, in my opinion, demonstrated proof of concept of a healthy longevity approach.

Joan Mannick, MD:
I'm going to talk about improving the function of the aging immune system as a potential health span endpoint and the lessons we have learned with our mTOR inhibitor program in trying to do this. The COVID-19 pandemic has highlighted the dysfunction of the aging immune system. It is interesting because as drug developers, we focused on aging heart, aging brain, aging bones, aging muscle, but not so much on what we can do about the aging immune system. So, it is possible that improving the function of the aging immune system and thereby decreasing the incidence of infections, such as COVID-19, is a feasible health span endpoint for clinical trials. And, it is possible we could improve the function of the aging immune system by targeting one or more of the mechanisms underlying aging biology. I'm going to focus on the activity of the protein kinase mTOR, which plays a fundamental role in why we age in studies we have done looking whether mTOR inhibitors could enhance immune function in older adults. So, there is a lot of potential benefits of improving the function of the aging immune system. Clearly, it could lead to improved vaccination response and decreased infections. We know from the exploding immuno-oncology field that if we improve immune function, we can decrease cancer incidence, but also what's less well-recognized is you need your immune system to clear senescent cells. So, this could help with diseases associated with increased inflammation. And last, I mentioned this in the last session, there was a remarkable paper published in Nature this year, showing that if you age the immune system, it will cause aging of all sorts of different other organ systems, so the immune system itself may play a key role in aging.

We started by just saying, can we improve immune function and improve the response to vaccinations in older adults with mTOR inhibitors? We did two Phase 2 trials in older adults. We treated them for six weeks with unusual dosing regimens of mTOR inhibitors and looked at their immune function by assessing whether they responded better to a flu vaccine. In two Phase 2 studies we saw, yes, low doses or intermittent doses of mTOR inhibitors could improve flu vaccination response. We then said, why is this happening? What is the mechanism by which immune function is improving? We did non-hypothesis driven RNA sequencing in whole blood. What was unexpected is the vast majority of gene expression pathways that were upregulated in whole blood were type one interferon induced antiviral pathways. This wasn't what we thought was going to happen with mTOR inhibitors. This is important because a key element of immune dysfunction in older adults is deficient type one interferon responses to viral infections. And, one of the reasons that COVID-19, for instance, may be more severe in older adults is because they have deficiencies in this pathway. So, what is this response? Well, when certain cells in the body, like plasmacytes or dendritic cells, recognize viruses, they secrete this class of cytokines called type one interferons, which bind to receptors on other cells and induce the expression of hundreds of different genes that inhibit the replication of all sorts of different viruses. If you look at the replicative cycle of a virus like Corona virus, there are all sorts of different steps. These genes highlighted by the red stars are the interferon induced genes that stop all sorts of different steps in viral replication. The genes in green are the ones that are upregulated in older adults getting low doses of mTOR inhibitors. This should stop the replication of many different viruses.

So, we asked, can we use mTOR inhibitors to improve interferon induced antiviral immunity in older adults and decrease the incidents of viral respiratory tract infections, which are the most common viral infections that occur in older adults? We used in these studies a particular kind of mTOR inhibitor called RTB101, which is an oral catalytic site inhibitor of mTOR. There has been confusion in the literature because this was a compound originally developed to be a dual mTOR PI3 kinase inhibitor by Novartis, but Novartis found when you use this in vivo or in humans, it never reaches concentrations high enough to inhibit PI3 kinase. It's really just an mTOR inhibitor. What is also interesting, there has been some questions in the chat about the safety of mTOR inhibitors. The therapeutic dose we have to use of this and other mTOR inhibitors to enhance immune function are tiny. For this drug, it is 1/120th of maximum tolerated dose in humans. So, it has been very well tolerated in clinical trials in almost 2000 older adults. We did to a large Phase 2b and Phase 3 trial to say, can we use this mTOR inhibitor to enhance interferon antiviral immunity in older adults and protect them from lab confirmed respiratory tract infections. The Phase 2 was done at 652 subjects in five different high risk patient groups. What we found was that RTB101 dose dependently decreased the incidents of lab confirmed respiratory tract infections, but the people with COPD and current smokers were non-responders. We then had our end of Phase 2b meeting with the FDA. They said for the Phase 3, we want you to enroll everybody 65 and older who does not have COPD or is a current smoker. They said, even though we wanted lab confirmed RTIs for the Phase 2b, we are learning with you in this new area of what is the right endpoint for a drug that improves immune function and antiviral immunity, instead of lab confirmed RTIs, we want you to have a Phase 3 endpoint that just is based on patient symptoms because patient symptoms are relevant to how they feel and function, but laboratory confirmation isn't relevant to how they feel and function. So, the end point was respiratory symptoms that are consistent with a respiratory tract infection, irrespective of whether we could show they were due to a lab confirmed infection, and we missed this endpoint. Despite the fact that the Phase 3 didn't meet the endpoint, I think we learned a lot about what is the right trial design going forward for mTOR inhibitors and other geroprotectors to improve immune function.

One of the lessons we learned that was really important is that you can target aging biology safely, at least to date in older adults. Particularly, we found that we could use a low doses or intermittent doses of mTOR inhibitors, and we didn't see the side effects traditionally associated with much higher doses of mTOR inhibitors that are used in cancer and transplant patients, like hyperlipidemia and hyperglycemia. We also found that in every trial, even the failed Phase 3 trial, we can significantly upregulate this interferon induced antiviral response. So, there seems to be some benefit on the immune system of targeting this aging pathway. We also found that probably looking at the incidence of infections was the wrong endpoint. This upregulation of antiviral immunity seemed in both the Phase 2b in Phase 3 trial to have a greater treatment effect of decreasing severity of infections, which should be the endpoint going forward. Fourth, we found it didn't look like every virus responded to this upregulation of antiviral immunity. There was greater benefits for some viruses, such as Corona viruses relative to other viruses like parainfluenza virus. So, having a targeted viral endpoint, like infections caused by Corona viruses, is probably a better endpoint. Last, and I think this important, in all our trials, the greatest benefits seem to be in the oldest of the old. I think just saying “age 65 indicates you are old” is probably too imprecise, and probably a lot of people who are 65 and older have a normal interferon response to viruses, but the older we get, the more we get deficiencies in this particular response and the better treatment benefit we see. For instance, in the Phase 2b trial, looking at the percent of subjects to develop laboratory confirmed RTIs in placebo in blue and in RTB treatment cohort in gray, you could see in the people over 85 years old, this was a pre-specified endpoint, there was a 66.7% reduction in the incidence of lab confirmed RTIs versus a 19% reduction in people younger than 85. In the Phase 3, there were not enough people enrolled over 85 to assess, but we did a post hoc analysis of people over 75, 43.2% reduction in the incidents of lab confirmed RTIs in the RTB treatment group that approached statistical significance, but very little reduction in the people under age 75.

So, with all these lessons, we did a follow-on small pilot trial looking at RTB prophylaxis to decrease severity, not incidence, of a specific viral infection, COVID-19, in the residents of nursing homes the very elderly and residents of nursing homes experiencing a COVID-19 outbreak. 18 people received RTB101, 17 people received placebo. They were dosed for four weeks during the nursing home outbreak and followed for another four weeks. The primary endpoint that the FDA suggested for assessing COVID-19 severity in nursing home patients were the percent of subjects with laboratory confirmed COVID-19 with protocol defined progressive symptoms, hospitalization, or death. This was the result of this pilot trial, 4 out of 17 people in the placebo group developed severe COVID-19 and two died. Whereas, no one in the RTB101 treatment group even developed a symptom of COVID-19. This is a small trial that needs to be reproduced in a bigger, well-powered study, but it does suggest we are starting to refine and get at the right endpoints for geroprotectors for improving immune function. In conclusion, this program does provide evidence that targeting aging biology to improve immune function in older adults may be a feasible health span endpoint for geroprotectors. We also learned that we need a more targeted endpoint in patient population than what we were using in our Phase 3 trial, and this can inform how to design future trials. I think we also have to expect and understand there is going to be a learning curve for both sponsors and regulatory authorities, as we move into these new health span endpoints.

Alexander “Zan” Fleming, MD:
Joan, that is so amazing. Again, I think it was success. If you had used an endpoint that did not depend on symptomatic evaluation, you would have had a different result. And that is the key point, are we asking too much to have evidence that people are experiencing? Are they noticing

the benefit? We don't ask that of a cholesterol lowering drug, obviously, but in this case it made a big difference. That was a big hill to climb and you came pretty close.

Joan Mannick, MD:
I do think symptoms in the elderly is a tough endpoint because they have so many symptoms and they can have shortness of breath because they have heart failure, they have allergies, they have some COPD, they have a respiratory tract infection, it is really murky. So, that laboratory confirmation does help sort of get an endpoint where, if you're improving anti-viral immunity, you're more likely to hit.

Alexander "Zan" Fleming, MD:
In the interest of time, I know there are so many questions that people would like to ask Joan, but let's do go on to Mark Espeland, who is a senior biostatistician and responsible for helping to develop, I think, a very important concept, that is, a composite endpoint that could be used to support a therapeutic indication for preventing onset of one or several chronic diseases.

Mark Espeland, PhD:
Thank you, Zan. Much of my work has actually been in lifestyle intervention trials and there are many age related outcomes that have been demonstrated to be improved by lifestyle trials in large, randomized clinical trials. On the left is a Persistent Mobility Disability that was championed by Margaret Pahor in the lifestyle study. In the calorie study, I know that Dan Belsky is going to present later on, but it developed the index of clinical markers that was shown to be improved by caloric restriction. On the right is the Ken Rockwood Deficit Accumulation Frailty Index, which is a proportion of a long list of potential health related deficits that is exhibited by an individual. Each of these trials have been very influential in terms of affecting care. I think there is growing evidence that lifestyle interventions can slow down biological aging; they can reduce poly-pharmacy, reduce healthcare costs, increase function, and increase disability life years going forward. So, I think they are powerful medicines and I think they are a platform for us to look at other potential outcomes that might inform development of pharmaceutical approaches. Also, I want to point out particularly in multi-domain lifestyle interventions, there are so many underlying mechanisms that might play a role in this that it is very difficult to parcel out what might be important. I'm sure it is probably the case that no potential mechanism is universally important across all potential participants and probably none conserve effectively as a surrogate marker.

With many colleagues, including the leadership of Nir Barzilai, we developed the design for the TAME clinical trial. To do so, we gathered data from at least 4 large cohort studies, the Rochester epidemiologic project, the health and retirement survey, the bone health initiative, and the Health ABC cohort. What we did to gain experience was to look at the multi-morbidity indices across these different trials to see the potential impact on how these are measured, whether from EMR, self-report or through adjudication, and which participants might be more at risk. We learned from Health ABC that gait speed, as presented earlier, was an important way of enriching risk for progression multi-morbidity trials. So, the TAME study that we proposed, this is the primary outcome that we developed based on age-related chronic diseases. Part of our thinking for this was that maybe this might be attractive for review by the FDA. In the end, we decided that across 6 years we can cut up the trial in 3000-3500 at risk individuals. We felt like we projected that in the control group. The accrual of multi-morbidity indices would be on the rate of about seven and a half percent per year. We targeted 20 to 25% effect size and designed the trial going forward.

Now, of course, there are many issues with the composite outcome. As was mentioned earlier today, the FDA is very open to using composite outcomes in some conditions. Very popular is the four point MACE, which is myocardial infarction, stroke, hospitalized angina, and cardiovascular death. Most of these though, such as a four point MACE, are clustered around a presumed set of mechanisms and for TAME, the underlying sense of mechanism is biological aging, but it is a little bit difficult to make that more clear. We picked these out because we felt like they might be sensitive to metformin and we can make a case for that in literature. But, with any composite, issues arise that you could potentially have some positive benefits across some components and potentially some harm on others that might balance each other. Also, if you do hit overall benefit and composite, it is very difficult and unlikely that you will be able to attribute it to any one of the individual components. Some of the advice we got during the reviews of TAME was why not do clinical trials separately for each of these outcomes. And, of course, that would be a daunting exercise. It is very expensive because you have to do large trials. Part of the appeal of a composite endpoint is one can accrue outcomes more quickly. But, in doing so, part of the appeal of doing this all in a single trial is that one is able to look to see how these hang together in statistical modeling, that is looking at sheer parameter models in which you are looking to see if there is an underlying feature that directly drives the incidence of each of these components and that is sensitive to the intervention.

I want to go back to the Look Ahead trial. It was a multi-domain lifestyle intervention that featured caloric restriction, increased physical activity, nutritional counseling, and cardiovascular risk factor monitoring. So, a multi-domain intervention. We took a look to see if an index of multi-morbidity could be influenced by that intervention. You see over the course of an eight year delivery of the intervention, there was a marked intervention effect, strongest through the first four years when the intervention was most intense, intervention intensity tailored off afterwards. It was strongest among those that had less multi-morbidity and importantly, it was strongest in those that have relatively older age. So, we feel like this shows that within the context of randomized, controlled clinical trial, multi-morbidity is an endpoint that can be influenced and benefit can be demonstrated. On the right, I showed the slide earlier, is the Deficit Accumulation Frailty Index in the trial. See that also showed important benefits over eight years; in fact, some initial benefits. So, we are using this more and more in other trials as a potential intermediate marker that may be more sensitive initially to interventions compared to multi-morbidity, where outcomes might accrue a bit more slowly. We are not claiming that it is a surrogate endpoint at this point, but I think it is something that requires additional exploration.

Alexander “Zan” Fleming, MD:
Mark, that is so important, and we will have many questions. Let's first start with Sue-Jane Wang, who would be on the FDA side of statistical review of a proposal that involves a multi-morbidity endpoint. What would be the key features of that analysis to Sue-Jane that would convince you that it is not simply a slight of hand, that there is one endpoint that is driving everything else? What is your reaction to this particular statistical approach?

Sue-Jane Wang, PhD:
I guess the reaction I have is that this benefit that is shown and also the authors are using some index that combined multiple different components to show the benefit. I believe the authors acknowledge that the endpoint was not a pre-specified endpoint. I read the paper briefly today, as I just got the slides. It mentioned that multimodality index was not a pre-specified outcome and they acknowledged that this is an exploratory study. To me, because I have been working in the domain of an adaptive design—I oversaw all the adaptive design submissions in the last decade—

there are utilities that could be useful once the exploration is done enough that there should be just limited uncertainties. And for those limited uncertainties, they will be good places to design a confirmatory trial with minimum adaptation for a successful drug development. But not to elaborate too much, that is my reaction at this point.

Alexander "Zan" Fleming, MD:
That is very helpful, Sue-Jane. Let's switch over to Peter Libby, who knows something about MACE, another composite endpoint. What would be your reaction to this approach, which is analogous, but of course multi-morbidity is of a very different nature?

Peter Libby, MD:
We would be dead in the water in the cardiovascular arena if we didn't use composite endpoints, and we have made a lot of progress and I think advanced public health, which we have acknowledged is our joint goal here. I think that we talk about hard MACE and expanded MACE in order to subtract some of the softer endpoints. For example, in the Cantos trial, which was the first large-scale clinical trial that targeted inflammation in cardiovascular disease, we deliberately selected hard MACE, and that was myocardial infarction, stroke, or death as the endpoint, and excluded things like hospitalization for heart failure or revascularizations because they are softer endpoints and we knew that would be controversial. We were sort of first on goal and we were wearing armor plate from all the attacks we'd had through the years from other aspects of the preventive community because we had the temerity to propose that inflammation could be a target. So, we selected the hard composite endpoint and I think that managed to quell some of the unhappiness on the part of some of our critics. So yes, for composite endpoints, but select them carefully and try and narrow them down to the most defensible and hardest endpoints.

Sue-Jane Wang, PhD:
May I chime in to add the additional comments. The MACE endpoint comment that was just made fit very nicely into the discussion of this composite end point. One of the regulatory considerations for a composite endpoint is that we wanted to have an efficient trial. We wanted to have a small trial, hopefully the study does not need a large number of patients to study with. The composite would allow you to composite these multiple different endpoints together, so that you have a higher statistical to show the evidence if the drug really is working. And so, if you are going to be cautiously optimistic in designing a trial with a composite endpoint, making sure that not only you show the composite endpoint benefit, the medical division would also want to look at the individual component of the composite. If the individual component actually shows a detrimental, harmful effect, that is going to hurt this particular drug development. This cautiously optimistic idea that I was thinking of, which is more of a regulatory research, not yet as a regulatory decision-making, is that an adaptation could help you adapt on those pre-specified components where you had a serious discussion with the regulators and for those individual components, you really want to trim down to not too many, but those that are clinically relevant. The key word here is they must be clinically relevant in order for it to be part of the clinical benefit consideration. If a design can incorporate this adaptation concept, it may help you with a higher chance or the probability of success will be increased in a setting when the component has some basic knowledge, but may not have sufficient information for one to solidly consider that it must be of clinical benefit.

Alexander "Zan" Fleming, MD:
Thank you, Sue-Jane. Theresa, you have the last word in the drug approval step here. So, any reactions about this composite endpoint?

Theresa Kehoe, MD:
Obviously, we have seen composite endpoints and they can work. It is always difficult for the review team when one of the items in the composite fails. And then, what do you do in that kind of situation? I think when you are crossing various disease states like this, that the Phase 2 data will be vital to all funnel into a single Phase 3 trial. You need to get agreement from all the various divisions; the way we are set now, you need to get agreement among all the various divisions to the construct of the Phase 3 trial. But the Phase 2 data, making sure that the dose for each of these various different disease states is actually the same. Those are the things really important, that is all the background work that needs to go into things before you can get to a large multi-composite Phase 3 trial.

Alexander "Zan" Fleming, MD:
Theresa, thank you so much. And to all our panelists. We went through two hours and it flew by for me. I wish we had another two hours or more. We will do this in some shape or form again, but I can't thank all of you enough. This was just a terrific discussion.

- Edited by Thomas and Brontë

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Evolving Commercialization Targeting Metabesity Excerpted Transcript (cont.)

The *Evolving Commercialization* session discussed the following questions: How are companies entering the healthy longevity space? What new business models of commercializing healthy longevity are emerging? How are investors reacting to developments?

*What you read is an excerpted version of that transcript, edited for clarity. To watch the full session recording, click here. A summarized Q&A section is also included at the end of this article.

Moderators:
Joe Cook, Jr., Executive Chairman & President, NuSirt Biopharma; former Chairman & CEO, Amylin
Dennis Purcell, Founder and Senior Advisor of Aisling Capital
Ed Saltzman, Executive Chairman, Cello Health BioConsulting

Speakers:
Philipp Gut, MD, Department Head, Nestlé Institute of Health Sciences, Nestlé Research
Roman Kalista, MD, Co-founder & CEO, RxDiet
Jerry McLaughlin, MBA, CEO & Board Member, Life Biosciences, Inc.
Casey Means, MD, CMO & Co-founder, Levels Health
James Peyer, PhD, Founder & CEO, Cambrian BioPharma
Pietro Antonio Tataranni, MD, CMO and Senior VP, Life Sciences at PepsiCo

EXCERPTED TRANSCRIPT:

Joe Cook:
NuSirt repurposes pharmaceutical agents to enhance results. We started in 2013 with a company called NuSirt, essentially following some observations that had been made in the nutraceutical space. At NuSirt, we thought it would be great to explore repurposing existing pharmaceutical agents for improving metabolic dysfunction, with an eye towards having people live quality lives longer. And indeed, we were able to demonstrate useful benefits across a wide range through three very rigorously run independently supported clinical trials. These benefits included a number of conditions that are essentially associated with metabolic dysfunction, what we now call Metabesity. [...]

For the last eight to nine years, we've been raising money, conducting clinical trials, and producing data. We found that the traditional pharma space is just not terribly interested in the results, even with data. Big pharma companies said, “You are not going to build a brand or a franchise this way.” We have also had conversations with other folks. And for the most part, they're interested in optimizing their margins so that they can spend more money on the promotion side. Very few are truly interested in developing a randomized controlled trial for natural products and certainly not in repurposed pharmaceutical products. So, we've taken a slightly different approach. We believe what we have observed is consistent with what we're seeing emerge in the middle category of this continuum of markets. We think the most likely and logical players—and we are happy to have two representatives here today—are companies who come from another sector, such as food or other elements of nutrition, or maybe companies who have existing trusted brands who can introduce agents that will improve healthy aging using science-based solid claims.

We believe RCT (Randomized Control Trial) is required, but they must build on the legacy of their social capital with their consumers to build trusting products that can work. I mean, it is just going to be very hard for Pharma to drop down into this space. I don't think the margins are going to be at 90% Cost of Goods Sold. I also don't think that they're thinking about pivoting toward total wellness. Pharma is more comfortable developing medicines that deal with people's diseases, for which characterizations can be made. Conversely, on the other end, I think most people are happy with just spending more money on marketing and driving sales. So, I see this as an emerging opportunity. This place is where we have been as the conversation goes forward.

Ed Saltzman:
[...] More importantly, perhaps more significantly, to the business model challenge is the difference between reimbursed versus non-reimbursed products. We haven't spent a lot of time in this meeting talking about reimbursement versus non-reimbursement. There is a lot of speculation that goes on. At some point, we will, or maybe we won't, have to justify value for our interventions. You would think that just the idea of having healthy longevity is so painfully obvious as to how much money you'll save. But, I'm here to tell you the reality is that from the value and access side, that's just not true. Like it is with the FDA and the regulated space, everything will have to be proven in the unregulated space or less regulated space.

Even where they may not be reimbursed, there will still be a substantial burden of proof on claims. I'm hoping we'll have a chance to talk about this in a little bit. There hasn't been much coverage on value metrics... on how we value. One of the things that I see behind the scenes is a lot of: “Who wouldn't want this intervention? Of course.” But, the question is not who wouldn't want it? It is, who is going to pay for it? And in the US medical system particularly, who is going to reap the

rewards? What are the benefits? What are the challenges of proving value? We fundamentally use two value measures for pharmaceutical interventions right now, globally: quality adjustable life year and disability-adjusted life year. [...]

I think the challenge we are dealing with—whether it be regulatory, commercial value access, whatever it be—is that we are in a world in which the science of biology is moving faster than the business. We are getting more innovation in biology than we are in business models. For a long time, that was inverted. [...]

Dennis Purcell:
I was going to take just a few minutes and talk about the industry from a financial investor perspective. I don't think we have had much of that yet. And to me, it boils down to two questions, is there the money out there to fund the industry, and will investors invest in this space?

I come from a traditional life sciences or biotech background where the people who funded us, or so-called limited partners, were generally the State pension funds or University endowments. Today, a number of State pension funds are underfunded or have a lot of unfunded liabilities. It cut into university endowments because of COVID. A number of them are struggling. So, what they are trying to do is just beat the indexes and beat the returns from stocks and bonds. They invest in real estate or timber or hedge funds or venture capital. And you know, their expectation is that "we are taking a lot of risks and therefore, we want a commensurate return." They don't have the timeframe that is necessarily going to make them good investors for this industry because of their problems. They are trying to get capital back faster. This industry is not going to be able to give it to the market back in one second. But the industry itself, the life science industry, has been great in the last few years. COVID has taken an interest in the industry to a whole new level. [...]

And the question is, why are people still pouring money into the companies? This is what I want to drive home here today. I think it's all about returning the capital to the investors. It's about exits, and we have had a wonderful exit environment. In the last couple of years, you exit as an investor, you get your money back to your investors, either through making an offering of an IPO or a merger or acquisition. And we have seen plenty of both, and that has kept investors interested in continuing to fund the biotech industry. But, we have an additional element here that should bode pretty well for the Metabesity or longevity sector. Over the last couple of years, family offices and high net worth individuals have piled into the sector. Family offices and high net worth individuals have longer timelines. They are more patient capital. And there's a lot of them, both in the United States and around the world. These are new investors, not the traditional VCs that have dominated the industry for a long time. [...]

Jerry McLaughlin:
[...] I thought I would touch a little more on what was mentioned about the history of commercialization in Pharma, at least from my experience, having been with big and small companies.

There was a time before time in 1990 when the willingness to spend and pay for a marginal unit of incremental healthcare benefit was unlimited. It was pricing inelastic. For years, I never saw a question on whether we would make price increases. I said, "this price increase has to drive down demand." I was an economics major, and I was proven wrong year after year after year. And this went on throughout the 1990s. Innovation was a very loose term. I can remember it was

considered innovative if you took a product that was three times a day down to twice a day, and it was reimbursed and lauded as something great. But, I think what we have seen over time, continually, is that the requirement in terms of marginal benefits for increased unit cost or willingness to pay has changed dramatically.

It is a brand new world in which we live right now, and the commercialization and go-to-market strategies are very different. [...] The reality is there has been consolidation on the payer side and lots of power there. It's really like the toughest professor you've ever had. You hate him, but it makes you stronger and better. And I think it's making our industry stronger and better. It is forcing us to innovate. It is forcing us to think not just about a commercial strategy in terms of sales and marketing, but a value strategy. [...]

So, when I think about commercialization strategy, I think about it from inception. [...] Throughout the development, you constantly have to examine the product profile, which we call "target product profile." It requires discipline to know when to kill, right? If you start heading down a wrong road, the longer you head down that road, the more expensive and time-consuming; the opportunity cost is greater of getting back on track. You have to build that discipline into your commercialization strategy at an early stage. Also, I think over time, the external stakeholder group has changed tremendously and the focus has changed. There was a time we focused on key opinion leaders and prescribers, and probably that is about it. Now, we need to understand the patient, the patient advocacy groups, and their journey before we really can understand how to bring value. And then, very early on, we need to understand the payer journey. [...]

I think the other thing from a commercialization strategy that we can talk about today is "life cycle planning." What I mean by lifecycle planning is mapping out the future of your company. You can build that by platform and by product. [...]

Finally, we get this question a lot, "When is Big Pharma coming into the sector? They are sitting on the sidelines, but Pharma is one of the ships coming across. We are going to see them on the horizon. Well, I can tell you with fact they're there, they're looking, they're scouting, they're watching, they're reading the papers. They're there; they're paying attention. I know firsthand. We have folks who are in touch with us all the time. Big Pharma acts in their way. They will measure twice, cut once. They will take a long time, but once they make a decision, they will move very, very fast. I think they are intrigued, but it's a little bit out of the box of the standard plan of a disease indication... that standard regulatory pathway. They understand how to value that and where they want to place their bets. [...]

Pietro Antonio Tataranni:
As you can imagine, CPG (Consumer Packaged Goods) companies and PepsiCo look at consumer trends very intently. But, we also look at significant science and technology trends. My team at PepsiCo, which is called Life Sciences, has that as the primary goal. There are two trends that we have landed on because of their magnitude and their timeliness. One is personalization. We can have a lot of discussion on personalization, but that is perhaps for another day. The other one where we have stopped having arguments inside the PepsiCo organization is healthy aging. We see the convergence of multiple organizations looking at healthy aging. [...] Healthy aging is going to create a tsunami, which in turn translates into a large marketplace. So, the question becomes not whether to discuss this anymore or whether this is an opportunity or not, but how you access it. You have to do two things from our point of view to access the commercial potential of healthy

aging products. One is to reflect on whether you have an offering to bring to that marketplace. Certainly in our case, we have products; but also, you must have an idea of how you talk to that segment of consumers. This is easier said than done because people don't like to be told that they are old.

There is an interesting concept of biological age versus chronological age. It is a way of moving the needle of the conversation a little bit more. And one of the insights that we learned this past year is that when you talk about biological age, that conversation is of interest to a much broader age range than anticipated. Reducing biological age is possibly even more attractive to younger people than it is to older people. [...] If you want to deploy a solution at scale for healthy aging or to improve healthspan... it cannot be high tech, high cost. It has to be low tech, low cost to have an impact of the magnitude where you touch as many people as you can.

Now, my opportunity as the Chief Medical Officer of PepsiCo is to be in an organization that puts a product from our portfolio into the hands and mouths of consumers a billion and a half times every twenty-four hours. So that is the scale of the denominator that I can access through this position by advising my leadership to go in this direction. It is obviously a great responsibility and a great privilege, but it's also a massive opportunity. And when you think along those lines, people are going to have to make choices between food or medicine.

I think that the solution that you bring into this marketplace of healthy aging has to deal with the three A's: affordability, accessibility, and acceptability. I'll make the point that when you talk about food and even food as medicine, we have to be very careful because people don't identify food as a prescribable intervention. [...] What large corporations are doing with their portfolio is recognizing that this massive epidemiological trend is a multi-year—in fact, multi-decade—effort to market their portfolio.

I have a few examples of reducing the impact in our product portfolio of certain nutrients, such as sugar reduction, sodium reduction, and using healthier oils to prepare our products. It is very contemporary. In fact, as of today, the FDA has come out with new guidance for a recommendation on how to reduce sodium in the majority of the food categories here in the US that will create another level playing field where the food and beverage companies will compete to best position their products in that landscape. When you reduce sugar and salt and improve your oils in your portfolio of products that reach a large number of people, this is bound to impact health and therefore, longevity. And so, just continuing to do this might be the lowest possible denominator of what a solution for this problem looks like.

But, at PepsiCo, we have gone beyond that. We will continue diligently and transparently to execute our product portfolio evolution and renovation. As I said on previous occasions, and I repeat, we want to go beyond this. We have started to look deeper at the science of healthy aging. We even created a process that didn't exist in the company before, which goes in our lingo by the name of “R&D Innovation Dossier.” This is where we consult with worldwide experts, try to understand the biology of what food and beverage might contribute in terms of improving health, and then go and look for potential solutions. [...]

Philipp Gut:
[...] Nestle global is the biggest food and beverage company in the world. If we think about aging, we have to think on a global scale, which also means aging is very different culturally.

[...] I will start with something a little bit provocative in saying that Nestle pioneered aging research. This goes back to the early two-thousands, actually to our pet care business. I'm not sure a lot of you know this, but we have a pet care business. They published in early 2000s that a restricted caloric diet extends healthspan and lifespan in dogs. There was a 14-yearlong study. This research started when I was six years old. This is the era before what we today consider modern aging research. Until today, it's the only higher mammalian example of extending lifespan by caloric restriction. [...]

Suppose we now shift a bit to the portfolio for healthy aging. That is what I would call a more traditional portfolio, which is looking at people 65 plus, especially those at risk of frailty, potentially even at the risk of malnutrition. There are great products, protein, and micronutrient supplements, but it's a bit of a traditional view on aging, where we think of the old, the frail person. But, I think Antonio said this beautifully, aging is just not the older segment. It comes really into a young segment, and it gets younger and younger. If you go to areas like Silicon Valley, it starts with young software engineers thinking of healthy aging. I think it is hard to put a limit on this market. We wanted to recognize that there is so much cool aging research and evidence about fundamental pathways of aging that we need to go one step further than the traditional products for frail and older people. [...]

James Peyer:
[...] Cambrian focuses entirely on FDA-regulated therapeutics that will ultimately be used for prevention. This is the class of drugs that we call geroprotectors, which can extend the healthy lifespan of animals, including humans. Then, the specific subclass of those that are going to be FDA approved in the same way that Lipitor is approved to prevent diseases of aging. In the case of these geroprotectors, they will be affecting multiple diseases of aging. That is the kind of products I think of as being in this longevity biotech space.

Once we have defined what we mean by the longevity biotech space, then we can talk about what, in my view, are the key challenge of this space. If you go back five years, I think the key challenge of this field was finding its legs for an investment thesis at all. There were so many programs, i.e., some interesting piece of fundamental biology was shown to extend the lifespan of a mouse. Then, we said, “Hey, we want to set up a biotech company around this, maybe even get some funding.” But then, we hit a wall at some point in determining what to build, such as a clinical program around that topic. I think that the field, as a whole, has moved past that.

We have come up with this idea that I refer to as, everyone has their own name for it, but I call it “stepping-stone indications.” Figuring out which disease indication in the here-and-now can be targeted with this interesting insight into the fundamental biology that also happens to slow down aging and then building a biotech company around just that piece. I think that the industry, as it is gearing up now, and what is going to be commercialized out of this field in the future is not so much geroprotectors (things that will slow aging) as drugs for diseases X, Y and Z, which also have the potential to slow aging. These drugs will be approved for diseases X, Y, and Z. I see the longevity space evolving as an industry of drugs created from insights into the biology of aging.

There's going to be a pivot point sometime in the future. My guess is it's going to be towards the end of this decade where we stop being an industry around insights into the aging field and start being an industry that is commercializing things that are actually going to be slowing aging. I think that's kind of the fulcrum point for this whole field taking off. My view is that the fulcrum point is going to be defined by the FDA's acceptance of the first surrogate endpoint based on

clinical trials because the problem with running a clinical prevention trial right now is that you can't run a short trial. Therefore, no serious biotech outfit is signing up to run a prevention trial for multiple diseases. And so, by having a surrogate endpoint, getting the okay to run a three-year trial instead of a ten or fifteen-year trial, you're going to get a lot of players, including us, entering this space. [...]

Casey Means:
[...] The Levels Program is closing the feedback loop between what you put on your fork and what is happening in your body so that you can personalize choices to optimize wellbeing, optimize longevity, and minimize chronic disease risk by stabilizing blood sugar. [...] Our mission is to reverse the metabolic crisis, which is, in many ways, a longevity crisis since metabolic diseases underlie so much of premature mortality. We are doing this by expanding direct-to-consumer access to personal health data, so that people can understand for the first time how food and lifestyle are affecting their bodies. [...] We are moving away from the reactive sick care model of monitoring and tracking once we have an illness to monitoring throughout our lifetime and never reaching that diagnostic threshold for disease.

[...] I believe that tools that help people improve their metabolic biomarkers, understand them, and optimize them will emerge as massively high value. High blood sugar is a root cause underlying many, even most, chronic illnesses in the US. It is estimated that 90% of our healthcare costs are related to chronic disease. The data is still needed to be shown whether these tools are preventative and do generate value. I think philosophically and logically we would see that value only if these tools can shift behavior. We believe that it's going to come down to behavior change over anything else. You know, pharma or healthcare interventions are foundational, but it's going to come down to behavior change.

I, as a physician, believe that you can't fix the cellular biology of aging without changing what people put on their forks and what they eat, day in and day out, every single day. [...] I think we are going to see some bottom-up shift in consumer decision-making, as people are more aware of how things affect their health. We see large populations getting results by knowing how food products are affecting their bodies. That's going to create a totally new world of demand for products. I think we can create some positive shifts for promoting healthy products and a more preventative approach in both the food and healthcare system. [...]

Roman Kalista:
[...] RxDiet looked at the problem from a little different perspective; instead of increasing the healthspan of all, we are trying to lift the bottom up. We focus on very difficult, unengaged patients. We look at the insurance claims data showing what payers end up actually spending on patient groups. It is interesting to see what payers say and what works everywhere, especially with health plan members. We know that about 50% of healthcare costs for each payer are incurred by about 5% of their member population. So, we look at that problem and try to analyze how can we reduce those costs. We know that CMS is going bankrupt pretty soon. We need to do something about our most expensive patients. What we specifically look at are metabolic diseases, diabetes, uncontrolled hypertension, et cetera. We looked at interventions that work, and not surprisingly, of course, the best intervention is on the number one list in most clinical guidelines: dietary change and exercise. We looked at options to make dietary modification and exercise prescribable. We have discussed dietary prescription, but we know it is extremely difficult. There was not any innovation for a while.

We focused on solving the problem of prescribing diet to this very risky population, usually called “the unengaged.” We know that these patients are very difficult to reach. They are very difficult to convince to do anything and especially change their diet and lifestyle. But, we also know that if we manage to do that, there are very significant healthcare savings to be realized by the payer. We understand that these patients cost on average $60,000. And if we focus on specific groups, we are somewhere in hundreds of thousands of dollars per patient. We know that there are interventions that work well. An example of this is a concept called food pharmacy, where these patients would receive a voucher from their provider and they would visit a local food pharmacy set up in their local hospital. They could pick up free food and they would have a conversation with a dietician. This simple concept works amazingly well. [...]

There are two major problems with setting up a food pharmacy. They are very local. You can usually reach people within about a 10-mile radius, and they are very problematic or expensive to set up, and they're almost impossible to scale. [...] We have looked at the most efficient way to distribute food nationwide. Of course, existing retailers do their job very well. Walmart can reach 90% of our population with a pickup option. They have been phenomenal in terms of the supply chain and their cost of food is extremely low, as is their costs of delivery. They can deliver food to your house for $2.50. This is unbeatable.

The second point was the actual cost of food. We came up with a very interesting mathematical problem to design a personalized meal plan for a person, a set of grocery products that you can give that person that is medically tailored to their condition. Designing a food plan according to their tastes and preferences is a very cost-effective but complex mathematical problem. The number of permutations is extremely high. The complexity of the problem is about 72 factorials in our cases, as we have designed it. It takes about three years to solve with a 16 core server machine. We were surprised that there is not a simple way to solve it. We have looked at deep learning solutions. Just recently published, Deep Mind has made great progress in this space. And surprisingly, these algorithms are pretty good at solving strategic games and strategic approaches to solving different problems, such as chess, a game of Go, etc. So, we have designed the meal planning program as a game for the algorithm to solve. And suddenly, we have been able to solve the large problem of 72 factorials, not in three years, but in about five minutes. That allowed us to build these patient meal plans and deliver them at the lowest possible cost in any given location in the United States. We currently have custom integrations with Walmart, Kroger's, Fresh Direct in New York City, Amazon Fresh. And we are now able to offer a product to a payer that is zero cost to start compared to a food pharmacy that can begin immediately. We can start with five patients; we can start with 5,000 patients. It doesn't matter much to us in terms of technology. We are able to deliver out foods to any of their patients.

The model that we are proposing to payers is that you pay for patient food. You take the risk on the food and we will take the risk on the services provided, whether with our care team or with our technology. After we realized the cost savings for the patient, we will have a shared savings contract to generate revenue per each successful patient. [...]

Ed Saltzman:
[...] Start with how you think the proponents of drugs for diseases are going to embrace this space or how they will approach this space? And then, how do they interface with today's tools and the fascinating tools and platforms that for instance, you have Casey and you have Roman. I'll throw that out as a general discussion point and ask my moderators to refine that or ask an entirely different question.

Joe Cook:
[...] I was with Lilly for 28 years. [...] We had a pretty good smorgasbord of ideas with absolutely no improvement in valuation. [...] I think it's going to be a very hard hill for pharmaceutical companies to digress from that margin evaluation calculation. That is why I said in my opening slide, I think the more logical players are those who are either consumer packaged goods companies or data science companies or perhaps biotech if it has got long enough investment horizons, that can go after that middle sector. [...]

I think we are operating in a culture today where there has been a substantial erosion of trust on almost every meaningful institution that we use to hold up and say we can count on it. [...] Who do you trust? We will have to go back to a position of trying to establish that trusting relationship with consumers or customers you already have and extend what franchise you do have and build on that basis. I don't think large Pharma is going—they may accept it if the margins get better—to move in that direction intentionally. They may explore it for curiosity, but I don't think they will do it long-term.

James Peyer:
[...] I spend a lot of time talking and thinking about this new world of medicines for promoting healthspan. It is going to look an awful lot like traditional biotech companies. We have actually had quite a lot of interest from traditional pharma investors who want to take bites at the apple for our different programs. We are even in talks to bring some programs that have an interesting biological activity related to aging out of big pharmaceutical companies to house them in biotechs because they don't quite know what they want to do with that asset. I think these will mature similar to how rare disease companies are developing right now, like oncology companies. I think the key point to nail the healthspan promise of these medicines is to have an institution that will be extremely long-term and dedicated to the healthspan mission. [...]

Philipp Gut:
I want to pick up on the term “unregulated versus regulated” because I think in the end it is not black and white, and there is no Pharma and other stuff. [...] Do we want to go into this field of healthy longevity, all the way to clinical trials, which cost a hundred million dollars to be able to say it treats aging, which today is not even possible from a policy perspective, or do we build the evidence otherwise? I think the future here is that some supplements will make it because they have the credibility. You have to build credibility with the healthcare professionals because those are the ones that recommend. Today, we often get feedback from medical doctors that they don't even know what supplement really to recommend because they essentially tell their patients to just buy something that is the cheapest because then there is good quality, but I really cannot tell you more. So, in the end, it is about the credibility. Then, if you think from a perspective of a fast-moving consumer goods company, aging becomes so important. Today, look at Nestle. We have a huge portfolio for the first five years of life, baby formulas and so on. The reality is that we have more people over 65 than children under five. Even the elderly or the older adults, they move into e-commerce. In e-commerce, you have very different ways to bring information to the consumer. In the end, it will come down to credibility, information, and how to bring it; and not whether it is a pharmaceutical or a nutraceutical or something else. [...]

Casey Means:
I just wanted to comment on a few things. I think the first one is the poor results we have maybe seen with large-scale behavior change tactics and whether that is a bad sign for these technologies,

like what we are talking about with Levels and others. Some historical thoughts on that… so, first of all, in the nineties when we changed the food pyramids and we said we were going to lean into six to eleven servings of carbs and grains per day and decrease fat. We saw the food industry really move in that direction. People actually did it. People started eating more carbohydrates and less fat, and we saw a resurgence of obesity, diabetes, and other illnesses related to this dysfunction and glycemic dysfunction. So, I think we don't give people enough credit for actually doing what people say and recommend. Unfortunately, that advice on low-fat diets was poor and it led to the situation in which we are in now, where 70% of food in the grocery store has added sugar because we had to replace the fat with something and the sequelae of that. I am hopeful that if we really get on track with a large-scale policy and perspective from the healthcare industry on a rational nutritional approach, it will trickle down and people can shift, and the food industry can shift. Because we have seen that happen already once.

Also, on behavior change, I think something we are seeing now that we have just never, ever had before is the closed-loop biofeedback on nutrition that sensors and wearables and new technologies, like direct-to-consumer lab testing, can do. We eat about a metric ton of food per year and multiple pounds of food per day. It is a lot, and to draw conclusions about "oh, this aspect of my diet is the thing I need to shift to have really a large gain." We have never had that possible. The idea that we would go to the doctor and they would say our fasting glucose is up by five points since last year… how in the world do you track that back to particular components? You have eaten thousands of things that year and made a change. In fact—and we are seeing this in our members—there are a very select amount of things in the diet that are the bombs causing the problem that you can adjust really easily. So, that closed-loop biofeedback can have a massive, really quick and efficient shift on behavior and creating the one-to-one relationship between food and outcome.

I think something interesting that James was talking about earlier was how clinical trials for longevity and whatnot, they are going to have to show earlier biomarkers, that you can find differences in within a few years as opposed to 10 or 15 years. But, the more we can shorten that to minutes or hours, like seeing biomarkers metrics change rapidly and then compound over time as a proxy for long-term clinical outcomes. I think that is really positive. We now have the ability to do that. I'm very hopeful for the behavior change side. […]

Roman Kalista:
I want to say that I think food, lifestyle, exercise, and pharma will always be complimentary to a successful treatment. […] I think there are a lot of things wrong with the food system as it currently operates, and just shifting that along—changing the public perception a lot—could move the needle significantly.

Antonio Tataranni:
[…] Where this discussion might diverge in terms of a solution is whether these are niche applications that go to a certain portion of the population, perhaps falling back into the trap of the sickest, the most needy, the ones that consume the most resources, or whether we are talking about deploying solutions at scale to benefit the majority of us because people aging and hopefully in a healthy way, is people looking like us. You don't have to go very far to find your target population other than this wonderful panel of experts. That is where, as somebody who has lived four-fifths of his career in pharma, I have been humbled by coming into food and beverage into the thought that when you try to deliver an application through that lens, this hyper medicalization of the problem works against you.

People don't eat science. People eat good-tasting foods that they like and have liked for a long, long time. So, first of all, you cannot take your consumer and jerk them in a different direction overnight. You have to be part of that journey and accompany that journey. But, the point that I want to make is that when you look at it through that lens, I think the biggest blind spot is that we think of health and fun as two opposite things. [...] My thought-provoking message to this panel is that if we were able to hide health behind fun, probably we would be much more successful.

Joe Cook:
I hope Casey, we are successful at doing changing behaviors with biofeedback. That would be a dream. I struggled mightily when we were trying to develop medicine for people with diabetes to get them first to agree that we could help them live a more normal life. Unfortunately, the recommendations of diet and exercise were listened to by 10% or less, and they stuck for maybe a month or two or three, and then people reverted. What I was more interested in is trying to figure out a way to activate the 80 plus million people in the United States who have some degree of demonstrated insulin resistance or glucose dysfunction. To me, that was the curve that I thought we could tip. We spent a lot of time trying to psychologically alter their attitudes. People don't want to be classified as sick. They prefer not to be called a diabetic person; they are a person with diabetes. We got into this psychology and quite frankly, we got to a point where we were just trying to get people motivated to live a better quality life. I think, Antonio, I really do think if we could hide health behind fun—and maybe we can do it by making the biofeedback loop fun or making the food delivered to your homes more fun, something that takes it out of "you are sick and I'm going to tell you how to live a better life" to, "I'm going to help you enjoy life and live it in a flourishing way, and by the way, you will probably enjoy more life"—that to me seems to be an integrated view of how to tie these together.

Ed Saltzman:
[...] I'm interested in your thoughts, Dennis, about where are the investible opportunities here that get you excited. How do you see those rolling out? Do you think this space is broadly ready for prime time? Do you see some of the traditional life sciences and VCs, who we have pointed out actually are sitting on an enormous amount of capital descending coming into embrace this field? What is your perspective?

Dennis Purcell:
James made the point of the investible thesis; there was not one ten years ago. I am not convinced I could articulate a good one right now. In biotech, there are a lot of "investible theses." I invest in early-stage companies; I invest in late-stage companies; I invest in oncology companies; I invest in rare disease companies. [...] We still have to define it [in healthy longevity products], I think. The public markets must be accepting it or the merger market must start accepting it or something because people won't invest in the industry if it is just an open-ended invest and this is cool, and it is going to take forever before it pays off, but it is a big deal and it is a big industry and all that kind of stuff. [...]

I think you have to have a line of sight on: are companies sustainable, what are some options they can do to get the money back, and how do we succinctly explain the investible thesis? Just to end on that Ed, this sounds kind of goofy now, but when we started, the entire venture industry was early-stage venture guys. We just said, we are going to be late stage; we are going to invest in phase two or phase three. And they said, well, venture guys don't do that. We made the observation that all companies don't have a straight line; they all fail in one way or another; they

all come back to earth; and they all need more money. That is where we want to play. That was the thesis that sold reasonably well for a number of years. Now, everybody is doing it. The thesis was clear; it was succinct; I could explain it on one page; and it was different. I think that is what we need to do.

Ed Saltzman:
One of the things that makes me think when I was listening to you, Dennis, these are remarkable lessons of history, is the fact that Pharma turned on a dime. I don't actually think Pharma is capable of turning on a dime, they probably didn't. But, in terms of relative Pharma history, I agree with you. [...] I think that what Pharma has been doing for the last several years, maybe more than that, maybe even close to a decade the way the time seems to fly, it might not be sustainable. It probably is not sustainable, given so many of the things we have talked about on this really fascinating panel today.

Joe Cook:
I predict you will see Pharma pivot on a dime if they are forced to negotiate prices with Medicare. I'm not sure it would be good for the R&D budget, but I guarantee you, they will not be able to sustain the structures they now have.

The participants in the Evolving Commercialization session had more to say. The Kitalys Institute Virtual campus gave them a Forum to express ongoing thoughts and insights. Join the Campus to read the messages they sent to each other post-session.

Q&A:

Q. Why are we not seeing the leading pharmaceutical companies entering the space of healthy longevity with geroprotective interventions?

A. Pharma is not competing in the healthy longevity space for several reasons:

1. Profit margin expectations cannot be met in intervention and preventative approaches. The margins expected by pharma and their investors are significantly higher than the returns on preventive approaches that they cannot incorporate preventives in their portfolio.
2. Pharma has a history of lowering value when stepping out of the disease and regulated space.
3. According to Joe Cook, NuSirt's addition of existing agents to pharmaceutical products to enhance results is not of interest to pharmaceutical companies because they are not sure of patent protection and have no interest in generally in repurposing drugs.
4. Pharma lacks the innovation to research and produce products based on cutting-edge approaches. Ed Saltzman says that innovation is not the industry's strong suit. He cites the rejection of alternatives to insulin for type two diabetes. Jerry McLaughlin and James Peyer are more optimistic and believe that Pharma is slow, but coming on the horizon. The drawback is that they do not know how to gauge value, but once they do, they will move quickly into the space.

Q. What business models lend themselves to success in the arena of healthy longevity?

A. Ed Saltzman opines that, "We are in a world in which [the science] of biology is moving faster

than business. We are getting more innovation in biology than we are in business models." Jerry McLaughlin says, “There is value in novel science." However, a company must engage in life cycle planning, understand its business model, and appeal to the payer, consumer and investors. In terms of the consumer or end-user, the better business model may lie in the unregulated space, particularly diet and exercise modalities, which may be better coming to market in the unregulated arena.

As a result, some models that fit well into the healthy longevity business environment include:

1. The food company model separated from the healthcare model, even within big food companies. Antonio Tataranni states that inside PepsiCo, "the question becomes... how you access it." Packaging, message, and outreach are a huge part of the business model. He suggests "hiding healthcare behind fun."
2. A scalable model. Antonio Tataranni addresses scale as follows, "it cannot be high tech, high cost. It has to be low tech, low cost to have an impact of the magnitude where you touch as many people as you can." As a new business model within PepsiCo, he cites the R&D Innovation Dossier that works with other companies and experts to research the science of food and nutrients in healthy longevity to create a line of evidence-based products that are consumer-driven and marketed with longevity focused value. Philipp Gut notes that Nestle already launched the Celltrient brand of cell health powders and pills. Thus, a business model evolving within the food sector is to take the helm in nutrition for health.
3. Direct to consumer model, such as subscription products and software programs and apps, like the Levels model.
4. Payer "rescue" model. DietRx focuses on behavioral change for the least engaged and most costly patients. Their value proposition is the reduction of costs to the payers by decreasing health costs for the unengaged. They offer outcome-based contracts. Roman Kalista tells us, “We can work with a self-insured employer or a managed care health plan. And these organizations are surprisingly very interested in food because they finally have the data and know that food insecurity and metabolic conditions are a significant problem for them. They cost a lot of money.”

Q. What will incentivize investors to put capital into the healthy longevity sector?

A. Dennis Purcell asserts that an exit plan for the investor is essential. Any healthy longevity company must consider merger or acquisition possibility, IPO, or other "investment back" exit plans from the start. Dennis Purcell sees potential new investors like high net worth individuals and family offices with a longer timeline than University endowment funds and pension plans, which must count on return regularly and sustainably. He also sees Covid-19 as a game-changer in that life sciences were focused on one disease at a time, not whole-body health. The Covid-19 experience showed that wellness, in general, is needed to withstand the ravages of a pandemic. There is now a more significant concern with overall health compared to a cure for a specific disease.

Jerry McLaughlin counsels new companies to start with their value proposition from the beginning. All participants agreed that the value to the consumer and therefore, to the investor of an intervention or prevention, is not as straightforward or compelling as a cure. It is important to plan around an exit strategy for the companies, investors, and shareholders on a solid value proposition, which includes protecting intellectual property, marketing, messaging strategy, and

data-driven methods that measure success from an investment perspective because all these impact company valuations. Jerry McLaughlin calls this "lifecycle planning."

Q. How do the unique challenges of payer coverage and fast-moving science impact commercialization, and are they related?

A. The clear drawback of uncertain insurance, government, or other cost coverage is erased in the pharmaceutical and regulated industry space. In the unregulated intervention space, the question of who will pay is critical. Jerry McLaughlin suggests that a company must look at the bottom-line support in cost savings for a preventive product, device, or optimistic behavioral change protocol.

Casey Means asserts that a business model focused on direct consumer offerings that help them know their biological responses to food and other stimuli is a high-value proposition: "I believe that tools that help people improve their metabolic biomarkers, understand them, and optimize them will emerge as massively high value [to payers]."

Roman Kalista reminds us that, "We know that about 50% of healthcare costs for each payer are incurred by about 5% of their member population... The model that [DietRx is] proposing to payers is that you pay for patient food. You take the risk on the food, and we will take the risk on the services provided, whether with our care team or with our technology."

A separate but related factor endemic to the healthy longevity space for commercialization is the speed of innovation and scientific breakthroughs, as well as the shorter exclusivity status of a product. Jerry McLaughlin warns, "Competitive environments are moving faster. The time of exclusivity, even for an innovator, is decreasing all the time. There was a time when, if you were the first in class, you had a five, six, or seven-year head start on everyone. That's now under three years."

Although coverage and competition may seem unrelated, they are closely intertwined. Payer programs and relationships must be cultivated. A strong approach is to have several platforms and multiple value propositions. In such a competitive, fast-moving environment, it helps to be a mission-driven company with a brand that resonates with both the consumer and the payer.

Q. How is the FDA affecting scientific research, getting to the market, and general business focus in the regulated space?

A. Jerry McLaughlin, whose company is in the preclinical stage of developing regulated products, asserts, "We are going to have to target age-related biology." We do not yet and may never target "aging" itself as a disease, instead regulated products should be developed to target related diseases and affect other hallmarks of aging. The approach is to show value concerning specific diseases and then make an expanded claim, developed along with disease-targeted research.

James Peyer states, "Cambrian focuses entirely on FDA-regulated therapeutics that will ultimately be used for prevention. This is the class of drugs that we call geroprotectors, which can extend the healthy life span of animals, including humans." He says that defining the healthy longevity sector is critical, and within that definition, regulated products for interventions also need explanation. His approach is finding geroprotectors that extend life and health within disease-specific therapeutics compared to curatives. He suggests that the bridge from laboratory to commercialization will be "stepping stone indications... Figuring out which disease indication in

the here-and-now can be targeted for a disease and also intervenes in fundamental biology to slow down aging, and then building a biotech company around just that piece." James Peyer's view is that the fulcrum point is going to be defined by the FDA's acceptance of the first surrogate endpoint based on clinical trials because the problem with running a clinical prevention trial right now is that you cannot run a short trial.

Casey Means interfaces with FDA by repurposing FDA-approved devices used in disease management for disease prevention: "Continuous glucose monitors that our members get are FDA approved for individuals with type one and type two diabetes. Levels represents and caters to emerging, strong consumer interest in utilizing these FDA-approved tools for a much broader population to give people the opportunity to manage metabolic biomarkers more closely before the emergence of disease. We are moving away from the reactive sick care model of monitoring and tracking once we have an illness to monitoring throughout our lifetime and never reaching that diagnostic threshold for disease."

Q. The Healthy Longevity space needs to incentivize consumers to affect their health significantly or obesity will exponentially jeopardize our nation's health. What modalities work and what is the responsibility of business to create and implement them?

A. Antonio Tataranni states that the solution you bring into this healthy aging marketplace must deal with the three A's: affordability, accessibility, and acceptability. He again suggests that the approach is not medicinal, but fun and sites that product packaging can effect acceptability.

Casey Means says, "We see large populations getting results [by knowing] how food products are affecting their bodies. That is going to create a new world of demand for products. We can make some positive shifts to promote healthy products and a more preventative approach in both the food and healthcare systems." Her conclusion is that individual, personal results will incentivize the consumer and drive the market.

Both Philipp Gut and Antonio Tataranni see the incentive strong in the younger markets. Philipp Gut points out that "aging is not just the older segment. It comes really into a young segment, and it gets younger and younger." Therefore, behavioral incentives are very different as you segment the marketplace and look at tastes, demographics, education, history, gender, ethnicity, and other variables that inform marketing design for other products.

Finally, incentives also require cost coverage, as the DietRx model deals with covered food programs. California is already giving food or meal plan coverage options in its entitlement programs.

Q. How can we change personal behaviors, such as diet, exercise and lifestyle that are essential to healthy longevity?

A. Antonio Tataranni sites the FDAs recent new dietary guidelines that reduce salt, sugar, and more oils. Moreover, behavioral compliance can be altered by emphasizing the positive aspects of right eating. Antonio Tataranni suggests making health-based foods, protocols, and practice more appealing through marketing.

Casey Means sites the guidelines of twenty years ago that fat be reduced in diets. She reminds us

that low fat diets garnered widespread adherence. Although the low-fat diet was counter to better health, as sugars were substituted to add taste. She uses the phenomenon to show how the public does change behavior in response to information. There is also a new world of devices for measuring and incentivizing better behaviors. They include biomarkers, wearables, and machines for bio-measuring. The Levels program emphasizes metabolic awareness through having people track their blood sugar continuously with a prescription wearable continuous glucose monitor, which has better outcomes as the incentive.

- Edited by Brontë

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Fireside Chats with Stephen Hahn, MD and Eric Topol, MD (cont.)

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Improving immune resilience and metabolic health to address the pandemics of infectious and chronic diseases.

Moderators:
Alexander Fleming, MD, Founder and Executive Chairman of Kinexum, USA
Lawrence Steinman, MD, Professor at Stanford University, USA
Lowell Zeta, JD, FDA & Life Sciences Counsel at Hogan Lovells

Speaker:
Stephen Hahn, MD, Former FDA Commissioner; Chief Medical Officer of Flagship Pioneering's Preemptive Medicine and Health Security Initiative, USA

Given the United States and global focus on treating diseases rather than preventing them, we must now find solutions to offset the economic and financial burden of chronic diseases. Dr. Hahn stated that, as noted in the Initiative's name, Flagship Pioneering imagines a two-part solution focused on health security and preemptive medicine. Relative to the health security aspect, the goal is to create a protective and predictive shield against potential health threats, globally and personally. Whereas, the preemptive medicine piece tries identifying pre-disease states in order to intervene early and prevent and/or delay disease progression. Dr. Hahn emphasized the importance of assisting people to become "empowered and invested in their health and wellbeing" because preemptive medicine is not only about drugs, but also harnessing diet and exercise to affect the trajectory of disease. Providing scientific rigor will hopefully advance this goal by helping to properly frame the message. Moreover, Dr. Hahn commented that Flagship is focused on ensuring these interventions are available to everyone, especially those with challenges to accessing healthcare. Dr. Hahn also analogized the necessity for urgency in preemptive medicine to what was present when Covid-19 emerged. Private sectors need incentivizing in order to increase motivation and involvement, which will subsequently encourage innovation. Flagship and other similar initiatives could create a framework and business model for preventative medicine that ensures these developments reach the underserved. This framework could disseminate knowledge, perform rigorous science, and work towards a more efficient regulatory pathway that does not require 20-30 years (e.g., surrogate endpoints and biomarkers). With all of these factors in mind, Flagship Pioneering continues to move forward with its Preemptive

Medicine and Health Security Initiative.

What will it take to increase healthy longevity?

Moderators:
Alexander Fleming, MD, Founder and Executive Chairman of Kinexum, USA
Lawrence Steinman, MD, Professor at Stanford University, USA

Speaker:
Eric Topol, MD, Founder and Director, Scripps Research Translational Institute, USA

Dr. Topol agreed with the concept that if a common thread to the aging process exists, then its discovery will be pivotal because studies reinforcing the possibility of modulating aging would have profound effects across an array of common diseases. Preventing and/or delaying chronic diseases is a fertile area for research in both the drug and behavioral spaces. For example, Dr. Topol commented that he exercises for 30 minutes every day and when he works with patients, he attempts to create treatment plans that involve discovering how each patient can achieve at least 5 days of aerobic exercise per week. The first step is determining the right time, type of exercise, and a way of making exercise a fun activity. Not only does exercise play a role in delaying cognitive decline and other diseases, but also so does diet. Currently, Dr. Topol and his colleagues are performing a 1000 patient study to help healthy people and those with type 2 diabetes determine their own individualized diet because there are only general guidelines right now and what constitutes a healthy diet varies from person to person. Dr. Topol believes the future of the anti-aging field includes taking advantage of what people are eating, along with other data, to help guide them and eventually prevent the contraction of diseases. While providing personalized data for prevention is complicated, it is the direction in which the field is heading and according to Dr. Topol, it is worth the effort. A challenge, however, will be the translation of compelling evidence in animal models that affect life and health span into human trials because human evidence has yet to be seen. Moreover, the results of such human studies must be validated and replicated before one becomes too excited about anti-aging drugs. Covid-19 has demonstrated the ability to quickly and effectively perform research and create innovation, which is an enormous triumph and should be replicated in preventative disease research. Additionally, digital health data systems used for identifying early onset of a Covid-19 infection demonstrate that digital health systems can allow for meaningful data accumulation on a large-scale and in a costly manner.

- Brontë

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The Fort Collins Connection (cont.)

Kate Norton:
I have lived in Fort Collins, CO since 1997. Prior to that, I would have claimed Evansville, IN as my hometown. My parents, two sisters and I moved a lot in support of dad's career as a food biochemist. I was born in Minnesota and then moved to Washington, Wisconsin, Maryland (lived behind Dr. Fauci) and Indiana. Even though moving often was difficult, it was a blessing because

it taught me how to make new friends and how to manage change. It also made it very clear that no matter where I was in the world, I could always count on my family.

Throughout my childhood, I was lucky enough to canoe and camp a lot with my family, travel, and participated in several sports including basketball, volleyball, ice skating, synchronized swimming and swimming. I was in band and orchestra, and still play the clarinet in local music groups. In high school and college, I was in the Indiana University German Honors Program and was able to study and work in Germany for two summers. I worked in an organic chemistry lab at Bayer Leverkusen. While on these adventures, English was verboten which, as challenging as it was, allowed me to truly learn the language. My father's side of the family was German, so it was exciting to connect with my family heritage in this way.

I attended Indiana University, earning a B.S. in Biology. I then went to the University of Cincinnati Children's Hospital Medical Center, where I earned a PhD in Developmental Biology using molecular biology and protein purification techniques. After some back and forth, my older sister persuaded me to take some time off after graduate school to relax, so I drove to her home in Fort Collins, CO in my tin can of a car stuffed with clothes and my chinchilla, Fledermaus. I lived in her basement, worked in her biotech patent law office and was lucky enough to get to bond with her two adorable children.

I was interested in the pharmaceutical industry even before graduating. My dad worked for Bristol Myers Squibb, so I knew a little about the industry. I learned about regulatory affairs online (back when there was very little online!) and became intrigued. Late at night in the lab, I would look up regulatory affairs job descriptions containing acronym after acronym. Every position needed GMP experience. Knee deep in DNA and RNA at the time, I couldn't understand why every regulatory position needed experience with Guanosine MonoPhosphate!!

My first regulatory job was at Atrix Labs, a drug delivery company in Fort Collins. Little did I know there would be extra fringe benefits: I met a handsome polymer chemist who would become my husband there! I helped secure European regulatory approvals of a human periodontal product (ATRIDOX™) through the Mutual Recognition process. Following European approvals, I became the post-approval change guru. I also worked with HESKA, a local animal health company, to support regulatory approval for use in dogs. This is where I was first introduced to Ann.

After Atrix Labs, I worked at PR Pharmaceuticals (see below) where I used my regulatory expertise in polymer delivery systems to support the development of microsphere products and prepare INDs, DMFs and Quality systems. I later worked at start-up companies in Boulder, CO focusing on the development of new chemical entities to treat various cancer indications. No longer excited about the long drive to Boulder, I eventually started consulting, which has allowed me to explore many different indications and technologies. I thoroughly enjoy providing start-up and virtual companies regulatory strategy and hands-on support to help them achieve their development goals.

My husband and I love to travel and recognize how fortunate we are to be able to explore the world. In 2015, we traveled to Panama to support an animal rescue started by a friend of mine. We slept in a room above Fiona the jaguar, who graciously woke us up every morning, and played with sloths just rescued from the Panama Canal Zone. We visited Noriega's tapirs and waved to Noriega himself every time we passed the prison where he lived. Just months before the new

Panama Canal was filled, we toured the canal and watched the huge gates being installed. I was given a spare bolt from the canal, so if it malfunctions, it's not my fault!

In 2018, we traveled with a friend to Kenya, where he has been working with a Kenyan company to provide clean water to schools for 15 years. The primary goal of the project is to help keep kids healthy and in school. While there, I learned that thousands of Kenyan girls (and millions around the world) drop out of school simply because they do not have feminine hygiene products. This is a tremendous loss of talent that most American women never have to think about. I discovered a nonprofit group called Days for Girls, International (www.daysforgirls.org) that supports keeping girls in school by providing washable hygiene kits and education. I now lead a team of over 30 talented women who have made close to 1000 kits, over 500 of which we brought to Kenya in 2020 (just prior to borders closing due to COVID). In addition, we have raised money to support a local Kenyan Days for Girls businesswoman who makes kits and distributes them in her area.

I serve on a church committee responsible for selecting an annual speaker for the Richard Hagen lecture. Richard Hagen is my dad, who passed away in 2014. He was a special man whose motto was to "always stay curious." For this reason, his friends established a lecture series in his name so that the community can learn about different religions, cultures and beliefs.

Ann Donoghue:

I was pretty sure I would be a mixed animal veterinarian in private practice when I entered Michigan State University's College of Veterinary Medicine. But, by my junior year, I realized I preferred the research side of medicine over the art side of it. I had summer jobs in a research lab performing HI assays for pseudorabies in pigs and testing potential vaccines in a BL2 animal facility. (I found that I really liked pigs!) I also interviewed for a summer job (but didn't get it) in the parasitology lab. I was keen to learn about every species. Fascinated by the data produced on dairy and swine farms, curious about the potential for preventive health programs for dogs and cats, amazed by the variability in wildlife species, interested in epidemiology.

MSU had a program where seniors could spend 1 to 3 months in a country that had foreign (to the US) animal diseases. I spent 2 months in Swaziland, observing foot and mouth disease vaccination programs, Babesia infections in dogs, food hygiene in the primary slaughterhouse that exported to Europe, horse breeding operations, wildlife disease management programs, and more. The experience and people were amazing and broadened my thinking. Graduation came soon after, and I needed to get a job (student debt!). However, I also needed to stay in East Lansing because my then husband was working on his PhD.

I accepted a graduate assistant position in the parasitology lab (the same one I didn't get the job in earlier!). One of the several projects I worked on became my master's thesis. I conducted a series of GLP studies in pigs to complete the major technical sections of two NADAs. So, as a graduate student, only about 10 years after GLPs were enacted, I was conducting studies that needed to be GLP compliant. I didn't really grasp the significance of that until much later! I also spent a year as the Section Chief of the Parasitology Diagnostic Lab when the current Chief took a leave of absence. I became a foreign language area studies fellow (hoping for research work in Africa) and took classes in African history and Fulani. But finally, graduation.

The company sponsoring the GLP studies I conducted hired me and moved me to New Jersey. There, I worked at the headquarters of Hoechst-Roussel Agri-Vet Company with a small, very experienced product development and regulatory affairs team. Fenbendazole was my drug and it

was approved or going to be approved in many species. Cattle, horses, dogs, pigs, cats, turkeys were all in my purview. I also worked on a product for honeybees and spent a lot of time in apiaries! While at Hoechst-Roussel, I skied in the Canadian Ski Marathon six times. The company was a major supporter of this cross-country skiing event and encouraged employees to participate. There was a friendly US-Canada rivalry each year!

After several years in NJ, Heska Corporation lured me to Colorado. There, I worked in animal health diagnostics, developing 3 heartworm lateral flow diagnostics and a Leishmania lateral flow. Heska went public, the focus changed, and I left to work with Claude Piché at PR Pharmaceuticals, Inc. There, the technology wasn't a drug, but a delivery method. We worked with biodegradable microspheres and several applications, such as heartworm prevention in dogs and weekly insulin in humans.

Finally, I went out on my own and began a consulting business; primarily helping small start-ups get on track with regulatory strategy, development plans, study designs and FDA interactions. An important project that I'm proud of was getting approval for the first drug to treat lymphoma in dogs. A Cinderella story for another time!

Besides all this work stuff, I had a Thoroughbred horse for 20 years (dressage, jumping), dogs and cats, a little aviary of zebra finches and lots of gardens. I play bassoon in local concert bands and an orchestra, and flute with a flute quartet (The Harmonic Ketones, spelling intentional, all 4 of us are scientists). I love to knit and am on my 47th pair of Knitted Knockers (look it up) and 3rd sweater.

Swimming has always been a love and a primary form of exercise, but I'm not fast and I didn't race (synchronized swimming in high school and college!). Open water is what appeals to me. Over the last 10 years, I've swum the Fort Collins Horsetooth Open Water 10 km Swim six times, swam in the inaugural Moroccan Swim Trek (4 days, 30 miles), La Jolla 10 Mile Relay and in the summer of 2021, I swam from Asia to Europe across the Bosphorus Strait and then a month later swam the English Channel on a relay team. (I got to be the relay leg who swam through a big bloom of jellyfish - no stings though!)

I serve on the boards of the Horsetooth Open Water Swims (a non-profit that raises funds for a local charity), the Northern Colorado Concert Band and our local veterinary medical association. I was president of the Northern Colorado Astronomical Society, and now write the newsletter for the Northern Colorado Amateur Radio Club. I recently got interested in ham radio (general license) and am looking forward to spending money on some fancy radios and antennas!

Ann and Kate:

After 7 years at Atrix, Kate interviewed with Claude Piche (who many of the Kinexers know!) at PR Pharmaceuticals. At the interview, Kate and Ann finally really met. We'd seen each other when Kate was at Atrix and Ann was at Heska – that periodontal product – but not worked together. Ann knew Kate's dad before she knew Kate – he was a talented trombonist in the concert band!

We found that we work together well. Together at PRP, we developed the quality systems, wrote many SOPs and set up the archive. We prepared for and successfully co-led the FDA preapproval inspection of a microsphere plant. We helped write and assembled an IND with a successful Phase I study completion.

We discovered that we play together well too. We swim, garden, bike ride and share holiday meals with each other and our families. Kate joined the band for a while, playing clarinet and we've even played clarinet-bassoon duos. We've both either paddled or swum in the Horsetooth Swim events. We've helped each other through hard times (both losing our dads in recent years). We continue to work together even as consultants… it's easy to do, we only live a mile apart!

Both individually and together, our Fort Collins connections are strong. We both feel quite lucky to be here and to now join the Kinexum team!

- Ann and Kate

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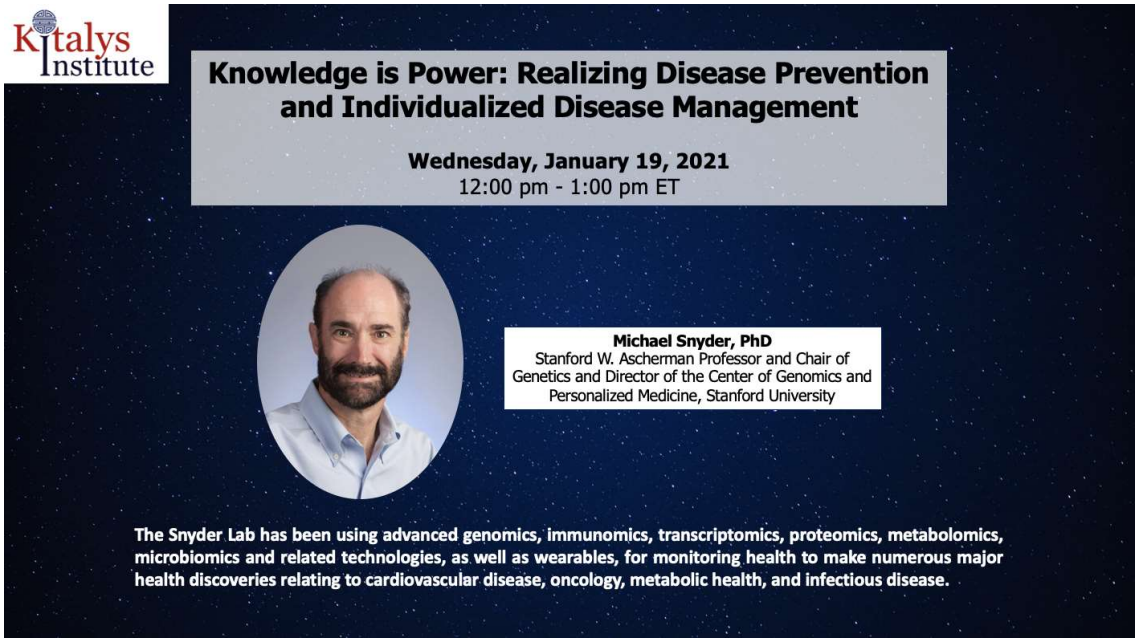

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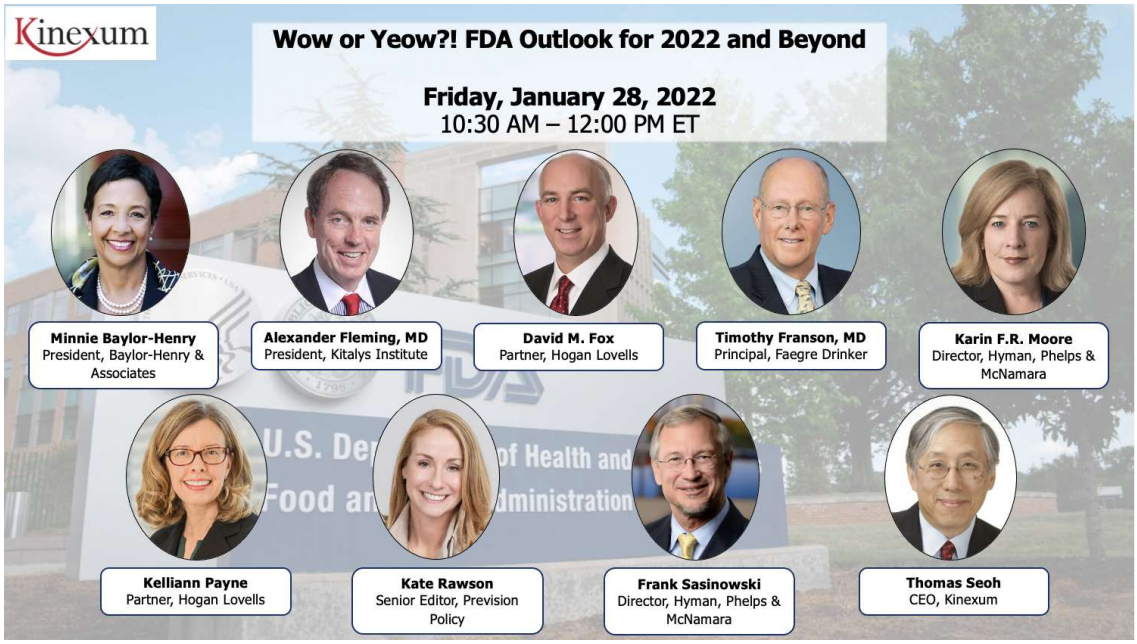

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