THE FOUNTAIN OF YOUTH? THE QUEST FOR AGING THERAPIES

HEARING

BEFORE THE

SUBCOMMITTEE ON INVESTIGATIONS AND OVERSIGHT

OF THE

COMMITTEE ON SCIENCE, SPACE, AND TECHNOLOGY

OF THE

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C O N T E N T S

September 15, 2022

THE FOUNTAIN OF YOUTH?
THE QUEST FOR AGING THERAPIES

THURSDAY, SEPTEMBER 15, 2022

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON INVESTIGATIONS AND OVERSIGHT,
COMMITTEE ON SCIENCE, SPACE, AND TECHNOLOGY,
Washington, D.C.

The Subcommittee met, pursuant to notice, at 10:03 a.m., in room 2318 of the Rayburn House Office Building, Hon. Bill Foster [Chairman of the Subcommittee] presiding.

U.S. HOUSE OF REPRESENTATIVES
COMMITTEE ON SCIENCE, SPACE, AND TECHNOLOGY
SUBCOMMITTEE ON INVESTIGATIONS AND OVERSIGHT

HEARING CHARTER

The Fountain of Youth? The Quest for Aging Therapies

Thursday, September 15, 2022
10:00 a.m. EDT – 12:00 p.m. EDT
2318 Rayburn House Office Building and Online via Zoom

PURPOSE

The purpose of this hearing is to discuss the state of geroscience, the study of aging and age-related diseases, and leading research efforts to develop therapeutic interventions that target aging and age-related diseases. The hearing will examine the ethical and societal implications that may result as aging therapies grow closer to commercial readiness. It will also consider the role of the federal government and barriers that may be affecting the research effort.

WITNESSES

- **Dr. Jay Olshansky**, Professor of Epidemiology and Biostatistics, University of Illinois-Chicago; Research Associate, Center on Aging at the University of Chicago; Chief Scientist at Lapetus Solutions, Inc.
- **Dr. Laura Niedernhofer (***KNEE-durn-ho-fer)*, Director, Institute on the Biology of Aging and Metabolism; Medical Discovery Team on the Biology of Aging; Professor, Department of Biochemistry, Molecular Biology and Biophysics, University of Minnesota
- **Dr. Steve Horvath**, Principal Investigator, Altos Labs

OVERARCHING QUESTIONS

- What is the state of scientific knowledge on the basic biological processes behind aging?
- What is the state of research on drugs and therapies that can extend human life?
- What outcomes in a formal animal or a clinical trial would represent the achievement of "anti-aging?"
- What are the long term ethical and societal considerations associated with therapies that could significantly extend human lifespans and/or healthspans?
- What is the role of the federal government in both supporting and regulating research on strategies to increase lifespans and/or healthspans?

Background

"Fountains of youth" have been a mythical concept going back to Herodotus. Many an entrepreneur has profited off spurious claims that their miracle product can turn back the clock on human biology. But researchers are working today on therapies that may legitimately be able to mitigate or even reverse the natural aging processes. A 2015 conference of biology and genetics experts reached a consensus that "there is sufficient evidence that aging interventions will delay and prevent disease onset for many chronic conditions of adult and old age."[1]

The term "geroscience" was first coined when the National Institutes of Health awarded a long-term interdisciplinary research grant to the Buck Institute in 2007.[2] Geroscience seeks to advance the study of molecular and cellular biology of aging and translate those fundings to age-related disease. A 2022 Symposium Report from the New York Academy of Sciences put it this way:

> *For many years, it was believed that the aging process was inevitable and that age-related diseases could not be prevented or reversed. The geroscience hypothesis, however, posits that aging is, in fact, malleable and, by targeting the hallmarks of biological aging, it is indeed possible to alleviate age-related diseases and dysfunction and extend longevity. This field of geroscience thus aims to prevent the development of multiple disorders with age, thereby extending healthspan, with the reduction of morbidity toward the end of life.*[3]

Scientists are still working to defining the field

The concept of **healthspan** is not yet defined by objective validated metrics, but one common definition is "the period of life spent in good health, free from the chronic diseases and disabilities of aging."[4] The innovation frontier and associated funding for geroscience is primarily focused on the extension of healthspan, rather than extending the human lifespan beyond the record set by 122-year-old Jeanne Louise Calment in 1997.

As scientists are still working to resolve a more discrete and quantifiable definition of "healthspan," success in geroscience today may be determined according to whether a therapy or drug can mitigate a wide range of diseases and ailments heavily associated with aging, even if those conditions are otherwise biologically unrelated. Statin drugs may already lower cholesterol and protect against heart attack or stroke, for example, but an aging therapy might mitigate the risk of heart attack, Alzheimer's disease, osteoarthritis, and hearing loss all at once. Geroscientists include both fatal and non-fatal but still life-affecting maladies among the target conditions to be mitigated with potential therapies. In regulating both clinical trials on humans and the marketing of prescription drugs in interstate commerce, the U.S. Food and Drug Administration generally takes a "one drug, one indication" approach. A clinical trial or a drug approval application would articulate a single condition to be addressed by a given treatment,

[1] https://www.researchgate.net/publication/275354743_Interventions_to_Slow_Aging_in_Humans_Are_We_Ready

[2] Buck Institute Awarded $25 Million to Establish New Scientific Discipline of Geroscience

[3] Extending human healthspan and longevity: a symposium report - PubMed (nih.gov)

[4] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6136295/

never a whole suite of conditions. As such, the small clinical trials being conducted now on some of the leading gerotherapy proposals generally identify a single target condition, but are informing the broader field of geroscience. For example, in 2019, in what may have been the first human trial for an aging therapeutic, scientists from Unity Biotechnology and Buck Institute used the target condition of osteoarthritis in the knee.[5]

Funding Support

At the federal level, many of the leading research efforts receive funding support from the National Institutes of Health. Since 1974, NIH's National Institute of Aging has supported intramural and extramural research on a broad range of topics associated with aging, including things like improving mental health in the elderly, treating Alzheimer's disease and strategies to prevent falls, but is increasingly supporting research on the basic biology of aging. NIA funds Nathan Shock Centers of Excellence in the Basic Biology of Aging at eight locations across the United States.[6] In addition, in October 2021, NIH launched the Cellular Senescence Network (SenNet), a Common Fund Initiative.[7] SenNet seeks to comprehensively identify and characterize senescent cells across the body over the next ten years.

In March 2017, the National Academy of Medicine initiated its Grand Challenge in Healthy Longevity. Its goal is to comprehensively address the challenges associated with global population aging and catalyze breakthroughs that will extend the human healthspan.[8] The National Science Foundation, primarily through its Biological Sciences (BIO) and Social, Behavioral, and Economic Science (SBE) directorates, has also extended grants toward the study of cellular senescence and other biological factors that influence the pace of aging.[9,10,11]

Over the last decade, a swell of private research funding has been committed to independent laboratories focused specifically on aging research, some of which issue their own extramural grants in turn. These include Altos Labs, the Buck Institute for Research on Aging, Calico Labs, Human Longevity Inc., the Salk Institute for Biological Studies, and the SENS Research Foundation. Some are non-profit, while others are for-profit. Some have received considerable attention in the media for the funding support they have received from American tech billionaires.[12] In addition, a number of independent biotech companies, some publicly traded, are also conducting research on specific therapeutic interventions to address aging. The larger, traditional pharmaceutical companies largely have not disclosed any active steps they might be taking toward the development or testing of new aging therapies.

Leading Research Frontiers

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[5] A Safety and Tolerability Study of UBX0101 in Patients With Osteoarthritis of the Knee - Full Text View - ClinicalTrials.gov

[6] https://nathanshockcenters.org/the-centers

[7] https://www.preprints.org/manuscript/202207.0160/v1

[8] https://nam.edu/initiatives/grand-challenge-healthy-longevity/

[9] RoL:NSF-BSF: (Dia)pausing aging. The role of vitamin D synthesis and signaling in the control of development, aging, and pace of life

[10] Brown Adipose Tissue, Biological Variation and Senescence in Humans

[11] Doctoral Dissertation Research: Cellular Senescence in Human Age-Related Mortality and Lifespan

[12] https://www.newyorker.com/magazine/2017/04/03/silicon-valleys-quest-to-live-forever

Recent leading research topics on extending healthspan include, but are not limited to:

Cellular senescence: Geroscientists hypothesize that senescent, or "zombie" cells, accumulate in the body as it ages, eventually causing tissued degeneration and age-related diseases. Researchers at the Mayo Clinic developed the first known senolytic drugs designed to clear out senescent cells. In a 2019 human clinical trial, these demonstrated that these drugs do boost proteins that help clear the bloodstream of senescent cells.[13] When senolytic drugs were used to amplify the protein *a-klotho* in lab mice, their lifespan increased by 30%.[1415]

Metformin trials: Metformin is a drug approved by FDA to treat Type 2 diabetes. Recent research suggests it may also ward off a wide-range of age-related maladies. Animal studies have demonstrated metformin extended the life span of worms, flies, mice, and rats, and observational studies of adults already taking metformin have found that it "appears to show protection against cancer, inflammation, and age-related diseases."[16,17] A research team led by the Nathan Shock Center at Albert Einstein College of Medicine is currently launching an NIH-funded clinical trial called Targeting Aging with Metformin (TAME), which will for treat human subjects with metformin to evaluate its effects on a range of age-related morbidities among a cohort of 3,000.[18]

Reprogramming: In 2006, Dr. Shinya Yamanaka identified a small number of genes within the genome of mice that can allow mature cells to return to an immature state, as stem cells. In effect, he found that cells are "rewritable," and was awarded the Nobel Prize for this discovery. In 2016, researchers at the Salk Institute for Biological Studies reported that it was possible for Yamanaka factors to be used to counter aging and increase life span in mice with premature aging.[19] In 2021, the Salk team, supported by a NIH / National Cancer Institute Cancer Center Support Grant, found that cellular reprogramming can be used to boost muscle regeneration and rebuild tissue in older mice.[20,21] This hypothesis has not been piloted on humans.[22]

Thymus regeneration: In 2019, researchers from Stanford and Intervene Immune published the results of a 9-person pilot study called TRIIM. They found that the natural decline of the thymus, a central immune organ, leads to the decline in overall immune competence with age.[23] They are now finalizing the results of a pilot clinical trial called TRIIM-X that evaluates proposed therapies for thymus regeneration. The study directors hypothesize that a combination of the

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[13] https://newsnetwork.mayoclinic.org/discussion/mayo-researchers-demonstrate-senescent-cell-burden-is-reduced-in-humans-by-senolytic-drugs/
[14] https://mcpress.mayoclinic.org/research-innovation/senolytic-drugs-boost-key-protective-protein/
[15] https://www.technologyreview.com/technology/anti-aging-drugs/
[16] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4772077/
[17] https://www.medicalnewstoday.com/articles/280725#Cheap-and-widely-prescribed-diabetic-drug-may-have-beneficial-effects-for-all
[18] https://pubmed.ncbi.nlm.nih.gov/27304507/
[19] https://www.salk.edu/news-release/turning-back-time-salk-scientists-reverse-signs-aging/
[20] https://www.salk.edu/news-release/new-study-shows-how-to-boost-muscle-regeneration-and-rebuild-tissue/
[21] https://www.nature.com/articles/s41467-021-23353-z
[22] https://www.salk.edu/news-release/new-study-shows-how-to-boost-muscle-regeneration-and-rebuild-tissue/
[23] https://www.nature.com/articles/d41586-019-02638-w.

prescription drugs metformin, DHEA, and somatropin will lead to thymus regeneration, which could in turn "potentially prevent or reverse key parts of the aging process more generally."[24]

NAD+ restoration: Researchers are learning more about the role of nicotinamide adenine dinucleotide ("NAD+"), an enzyme in cells used for energy metabolism, and loss of SIRT3, a mitochondrial protein, in age-related metabolic decline.[25] The Buck Institute for Research on Aging recently published a paper suggesting that many age-associated diseases can be slowed down and even reversed by restoring NAD+ levels.[26]

Biomarkers and identifiers of aging: The naturally short life span of model organisms evaluated in animal studies – worms, flies, and mice – make it possible to observe the effect of proposed aging interventions in a reasonable period of time. But as clinicians seek to translate these findings, it is not practical to wait for their human subjects to age over several decades to see how their aging interventions may have performed. Some geroscientists are focused on defining biomarkers of aging in human, such as DNA methylation, so that the effects of an intervention could be evaluated within months or just a few years. Well-established biomarkers will be key to efficiency and cost-effectiveness to carrying out larger clinical trials on humans.

Societal Implications and Long-Term Questions for Policymakers

Some researchers project that within the next decade or two, therapies that can add add ten years or more to the human healthspan will be demonstrated successfully in a clinical setting. Several of the proposed interventions being evaluated, such as metformin, are already largely low-cost and widely available. As such, commercial application of a clinically proven anti-aging therapy could ultimately be quite widespread. The implications for society would be substantial on:

- Demographic projections
- Healthcare costs
- The workforce
- Social security and other financial implications for retirement
- Health insurance

The advent of low-cost gerotherapies would also introduce philosophical, ethical, and policy questions, such as:

- What is the obligation of insurance companies to make gerotherapies widely accessible?
- What is the obligation of government to ensure the equitable availability of gerotherapies?
- Would a longer healthspan enabled by prescription drugs justify a later retirement age?
- When would it be appropriate for a physician to stop a patient's access to prescription gerotherapies?

[24] https://clinicaltrials.gov/ct2/show/NCT04375657
[25] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5088772/
[26] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7963035/

Chairman FOSTER. This hearing will now come to order. Without objection, the Chair is authorized to declare recess at any time.

Before I deliver my opening remarks, I wanted to note that, today, the Committee is meeting both in person and virtually. And I want to announce a couple of reminders to the Members on the conduct of the hearing. First, Members and staff who are attending in person may choose to be masked, but it is not a requirement. However, any individuals with symptoms, a positive test, or exposure to someone with COVID–19 should wear a mask while present.

Members who are attending virtually should keep their video feed on as long as they are present in the hearing. Members are responsible for their own microphones. Please also keep your microphones muted unless you are speaking.

And finally, if Members have documents that they wish to submit for the record, please email them to the Committee Clerk, whose email address was circulated prior to the hearing.

Well, good morning, and welcome to our Members and our panelists. One of the most important functions of the Science Committee is to help inform Congress of rapidly emerging technologies that will have important policy implications so that we're not always playing catchup. The past decade has seen progress in medical technology that would previously have been seen as science fiction. Not long after its discovery in 2012, I started getting increasingly urgent requests for meetings from cellular biologists telling me about the discovery of an incredible gene-editing technique called CRISPR. And that brave new world was not going to be a century away and might not even be a decade.

Many of us were here for the 2015 Science Committee hearing on the science and ethics of genetically engineered human DNA. In fact, it was only three years after that, six years after the discovery of CRISPR, that a Chinese scientist shocked the world when he announced that he had created the first gene-edited human child. We are still grappling with the potential societal, ethical, and economic implications of that breakthrough.

I believe that the aging therapies being evaluated by the geroscience community today may be equally seismic in their impact. The hypothesis at the heart of geroscience is that aging itself is a relatively small set of general processes, and that some of them may be malleable. It is a hypothesis that is reinforced by the wide range of aging processes observed in the natural kingdom. We didn't use to think of aging as a disease, but that may be changing. Rather than looking at individual conditions, the entire process of aging is being considered as a driving factor behind increasing morbidities.

And because of the analytical tools that have been developed through decades of federally funded research, scientists now have the ability to break down aging into a collection of biological events and are developing a deep knowledge about how it happens at the cellular level. They are making connections between these cellular changes and how they manifest as illnesses and pain throughout our aging bodies. They're learning that these biological events, at their most basic level, may be influenced by deliberate or even inadvertent intervention. And if you can do that safely, aging and the

goal of increasing healthy lifespan, or healthspan, may come within sight.

In just the past three years or so, scientists have started testing aging interventions on humans through small FDA- (Food and Drug Administration-) approved clinical trials. The first trials had fewer than 100 human subjects, sometimes fewer than 10. But right now, the Albert Einstein College of Medicine, with the support from the National Institutes of Health (NIH), is standing up a clinical trial with a cohort of 3,000 subjects to evaluate whether a prescription drug called metformin can actually help delay age-related chronic diseases in general. A formal trial like this that seeks to solve several otherwise unrelated diseases is relatively unprecedented. Imagine how profound it would be if we could identify a drug or therapy that can simultaneously mitigate Alzheimer's, cancers, macular degeneration, hearing loss, and joint pain with a single or a small set of treatments. Among those—among other things, this would have an enormous implication on the Federal budget.

Of course, we're not there yet, this field is still nascent enough that the leading thinkers are still sorting out some of the basic vocabulary issues. It seems like almost all of the serious research efforts are focused on expanding the human healthspan, not the absolute limit or duration of human life.

We will hear from our witnesses about the concept of healthspan today, but to be sure, the definition of healthy varies from person to person. If increasing healthspan is the goal, how will scientists know that they've done it? And how can the field determine the success or failure of an aging intervention without waiting decades to see how people fare as they age? If every experiment takes 70 years, this field will take a long time to develop.

If researchers are ultimately successful in translating the outcomes that they have seen in model organisms into humans, we will have an even—have even bigger questions to confront. For example, if you extend healthspan, do you also extend the lifespan and simply delay the protracted aging process to a later date? What happens to healthcare costs and the burden of our healthcare system? Would we see people in their 60's starting second careers? And what would that mean for the broader labor force? Can insurance companies charge your—change your premiums based on whether or not you take the aging therapy?

So we've all witnessed firsthand the breakneck speed of technological innovation in the country over the last 40 years, and so we should know better than to be caught unaware. Our responsibility as policymakers is to get educated today on a field of research that could soon lead to transformational change.

Our witnesses today represent the leading edge of geroscience, and I know that they will be faithful to the guidelines on our path to understand this topic and its implications at a deeper level.

[The prepared statement of Chairman Foster follows:]

Good morning, and welcome to our members and our panelists.

One of the most important functions of the Science Committee is to help inform Congress of rapidly emerging technologies that will have important policy implications, so that we are not always playing catch-up. The past decade has seen progress in medical technology that would previously have been seen as science fiction. Not long after its discovery in 2012, I started getting increasingly urgent re-

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The hypothesis at the heart of geroscience is that aging itself is a relatively small set of general processes, and that some of them may be malleable. It is a hypothesis reinforced by the wide range of aging processes observed in the natural kingdom.

We didn't used to think of aging as a disease, but that may be changing. Rather than looking at individual conditions, the entire process of aging is being considered as the driving factor behind increasing morbidities. And because of the analytical tools that have been developed through decades of federally funded research, scientists now have the ability to break down aging into a collection of biological events, and developing deep knowledge about how it happens at the cellular level. They are making connections between these cellular changes and how they manifest as illness and pain throughout our aging bodies.

They're learning that these biological events at their most basic level may be influenced by deliberate, or even inadvertent, intervention.

And if you can do that safely, aging and the goal of increasing healthy lifespan—healthspan—may come within sight.

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And how can the field determine the success or failure or an aging intervention without waiting for decades to see how people fare as they age?

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- Can insurance companies change your premiums based on whether you take the aging therapy?

We have all witnessed firsthand the breakneck speed of technology innovation in the country over the last 40 years, so we should know better than to be caught unaware. Our responsibility as policymakers is to get smart today on a field of research that could soon lead to transformational change. Our witnesses today represent the leading edge of geroscience and I know they will be faithful guides on our path to understanding this topic at a deeper level.

I thank them for joining us today and I yield to Ranking Member Obernolte.

Chairman FOSTER. I now request unanimous consent to include in the record for this hearing a letter from the Buck Institute for Research on Aging, and without objection, so ordered.

And the Chair will now recognize the Ranking Member of the Subcommittee on Investigations and Oversight, Mr. Obernolte, for an opening statement.

Mr. OBERNOLTE. Thank you, Mr. Chairman. I am so excited about this hearing. I'm excited for a number of different reasons. For thousands of years, mankind has been searching for the fountain of youth. And in the last several hundred years, it has become abundantly clear that the fountain of youth is—is going to be discovered not through exploration, but through science.

It is a particularly relevant topic for this Subcommittee to be taking up for several reasons. First of all, the fact that a lot of the research in geroscience is funded through the NIH and the NSF (National Science Foundation), which are governmental agencies that we have influence over, so it'll be very interesting to me to see some of the fruits of that investment. And that will better prepare us to make the argument for continued investment and maybe greater investment in the future.

But I am also interested because, as the Chairman mentioned, the implications of a longer human lifespan are profound in the fields of public policy and governance, both good and bad. And it behooves us to start having that conversation early as we prepare for the societal changes that will come as a result of a greater life expectancy in the United States.

But the third reason that I am so excited about this is because, in many ways, you can judge our progress as a society and a country by our average life expectancy. It's an indication not only of our prosperity, but also of the ways that we honor and treat our elderly. And if we can catalyze a future life expectancy and a future growth in life—in healthspan, the number of years that we have a productive, healthy living, we will progress not only as Americans but also as a human race. So I'm very excited to hear from our witnesses and very excited that this hearing has been convened.

Thank you, Mr. Chairman. I yield back.

[The prepared statement of Mr. Obernolte follows:]

Good morning. Thank you, Chairman Foster, for convening this hearing. And thanks to our witnesses for appearing before us today.

Aging is an inevitable occurrence for those of us lucky enough to live long enough to experience it. Since the phenomenon of aging began, humans have been exploring ways to slow down the effects of aging and extend human lifespan. This anti-aging mentality has strong roots in our culture—just look at the variety of skincare products on the market today or the title of this hearing. Throughout history, humans have always been seeking the "fountain of youth".

What we have convened to discuss with our witnesses today, though, is not how we can end the aging of human beings, but how we can extend collectively the period of healthy living, or health span. This means not necessarily extending the lifespan but extending healthy life before aging related diseases are able to take hold. If achievable, this could have huge implications on society, as the physical and mental effects of aging are slowed, and we are able to live healthy lives for a longer time.

Our witnesses today represent a variety of stakeholders who have been engaged on this topic in the scientific community. One common theme I have found from their testimony is their emphasis that geroscience, the science of aging research, is not focused on expansively extending human life to immortality. Rather, they are utilizing a number of scientific methods and techniques to uncover treatments that could generally slow the effects of aging and prevent the prevalence of disease in older generations as they age. The research they are doing ranges from the reversal of aging to isolating senescent cells to preventative therapeutics that can have across the board health implications.

I am looking forward to hearing more about these different therapeutics and treatments, but also about how traditional methods of living a healthy life by practicing good diet and exercise habits can play into this equation.

Federal investment into geroscience research has primarily been at the National Institutes of Health. In 1974, NIH established the National Institute of Aging to fund research focused on the effects of aging and examine the issue in depth. The National Science Foundation has also awarded grants focused on the study of senescent cells and biological factors that contribute towards aging. Additionally, I would be remiss to leave out the huge amounts of private sector capital that has been invested into aging research.

Aging is a topic that interests us all, as we all hope to live long and full lives. It is an interesting perspective to consider that this challenge of aging is really a challenge born from the success of living longer lives.

Thank you, Chairman Foster, for convening this hearing. And thanks again to our witnesses for appearing before us today. I look forward to our discussion.

I yield back the balance of my time.

Chairman FOSTER. Thank you. And if there are Members who wish to submit additional opening statements, your statements will be added to the record at this point.

[The prepared statement of Chairwoman Johnson follows:]

Good morning.

Thank you, Chairman Foster, for holding today's hearing on geroscience, a field with the potential to transform our society. A field which challenges what many have assumed is a universal truth—that aging is immutable.

The significance of what we will be discussing at this hearing cannot be overstated. I had a twenty-year career as a nurse, and from that experience, I know firsthand the challenges of compounding illnesses in seniors—on both the patient and on our health care systems.

I like to say that the Science, Space, and Technology Committee is the committee of the future. Today's discussion is just one more chapter in the Science Committee legacy of looking over the horizon:

In the mid-1970s, under Chairman Olin Teague of Texas, the Science Committee held the first hearings on the threat of climate change.

In 1979, the Committee under Chairman Don Fuqua of Florida took the first look at the opportunities and risks associated with technology transfer to China.

In 2010, Chairman Gordon of Tennessee led hearings on geoengineering, where the very notion of carbon removal was first introduced to Congress. Now, twelve years later, we have provided $3.5 billion dollars to the Department of Energy through the *Infrastructure Investment and Jobs Act* in order to stand up technology hubs for direct air capture.

Those previous hearings were important because they provided an opportunity to start needed public discourse on critical issues, no matter how futuristic they might appear. As one ancient Greek philosopher said, "the only constant in life is change." We need to be prepared for those changes.

If geroscience succeeds in its grandest promises, there will be a host of ethical questions to consider. This hearing gives us a chance to examine some of those questions. It also gives us the chance to set the stage for a productive and positive conversation on aging. For too long, aging has been a negative word or something to fear. However, we all age. We cannot stop time. I am pleased that the consensus in the scientific community is that we don't need to chase immortality. What we need to do is increase our healthy years and mitigate the health concerns brought on by age. And we need to ensure equal and affordable access to the tools and therapeutics that increase everyone's healthspan.

On the wall on our hearing room in the Rayburn Building is a quote from Alfred Lord Tennyson:

"For I dipped into the future,
Far as human eye could see,
"Saw the vision of the world,
And all the wonder that would be."

I am proud that today's hearing will once again dip into the future and try to see a vision of what's to come.

I yield back.

Chairman FOSTER. And at this time, I'd like to introduce our witnesses. Our first witness is Dr. Jay Olshansky. And Dr. Olshansky

is a Professor in the School of Public Health at the University of Illinois at Chicago, Research Associate at the Center on Aging of the University of Chicago, and Chief Scientist at Lapetus Solutions, Incorporated, a company he cofounded. Dr. Olshansky's work is focused on linking the scientific study of aging with investments in longevity and mortality-related projects—products. Additionally, his research includes exploring the health and public policy implications associated with individual and population aging. Dr. Olshansky is also a board member of the American Federation for Aging Research.

After Dr. Olshansky is Dr. Laura Niedernhofer. I hope I did that right. OK, thank you. Dr. Niedernhofer is a Director of the Institute of the Biology and Aging and Metabolism and Medical Discovery Team on the Biology of Aging. She is also a Professor in the Department of Biochemistry, Molecular Biology, and Biophysics at the University of Minnesota. Her research program is centered on the—studying fundamental mechanisms of aging and developing therapeutics to target them. She's also contributed to the discovery of a new class of drugs called senolytics. Dr. Niedernhofer currently serves on the Advisory Council of the Division of Aging Biology at NIA (National Institute on Aging) and on the Board of Directors of the American Federation for Aging Research.

Our final witness is Dr. Steve Horvath. Dr. Horvath is a Principal Investigator at Altos Labs and a tenured full Professor in Human Genetics and Biostatistics at the University of California, Los Angeles (UCLA). His research lies at the intersection of several fields, including epigenetic biomarkers of aging, preclinical and clinical studies in genomics and epidemiology. Dr. Horvath and his UCLA colleagues published the first epigenetic clock for saliva in 2011 and 2013. And he published the first pan-tissue clock, also known as the Horvath Clock. Recently, he presented a universal clock that measures age in all mammalian species. Great, OK.

And now as our witnesses should know, each of you will have five minutes for your spoken testimony. Your written testimony will be included in the record in its entirety. And you—when you have all completed your spoken testimony, we will begin with questions. Each Member will have five minutes to question the panel. And if we have time, we may have a second round of questions this morning.

And we'll start with Dr. Olshansky.

TESTIMONY OF DR. JAY OLSHANSKY,
PROFESSOR OF PUBLIC HEALTH,
UNIVERSITY OF ILLINOIS AT CHICAGO

Dr. OLSHANSKY. All right. First of all, I want to thank the Committee for the opportunity to participate in these hearings on what I consider a new public health initiative within—known within the community of scientists and health professionals as geroscience. The story I'm about to tell you is an easy one to communicate because all of us are experiencing aging firsthand.

In the modern era, most people in developed nations and a rising percentage of people in developing nations have the privilege of living a long life, a privilege denied to most throughout history. Pioneers in public health medicine and science from just a few genera-

tions ago gave us the gift of a long life. And since then, humanity has worked hard to maintain this privilege and extend it to others less fortunate.

Life expectancy increased from one year every one or two centuries for the previous several thousand years to three years of life added per decade in the 20th century. The chances of surviving to the age of 65, 85, and 100 have never been higher than they are now. There is reason to declare victory in the pursuit of extended survival, but plenty of work remains to ensure this privilege is made available to everyone.

This longevity revolution came with a price. The modern rise of cardiovascular diseases, cancer, dementia, Alzheimer's, and nonfatal impairments are byproducts of success, not failure. We just had to live long enough to see them. While risk factors hasten the emergence and worsening of these diseases, the biological processes of aging march on in the background, uninfluenced by treatments for diseases. Aging has become the most important risk factor for the diseases and disorders that occur today.

The quest for aging therapies discussed in this hearing is at the heart of a new public health paradigm that has been in the works for the last half century but which has gained traction just within the last few years. Here's the story in brief.

Changes in our cells and tissues occur with the passage of time. We call it aging. But there's nothing magical about this since we see the same process occurring in our pets and automobiles. It was suggested in the 1950's, 1960's, and 1970's that aging should eventually become the target of medicine and science, but too little was known at the time about how aging happens. Medicine and public health did what it could in the interim to devise ways to detect and treat diseases one at a time as if independent of each other. And this was a logical next step in dealing with the diseases that appear in aging bodies. But this approach came with limitations that can best be thought of as a game of Whac-a-Mole. Knock one disease down and another appears shortly thereafter. The longer we live, the shorter the distance between these diseases.

The science behind the "how" question in aging has advanced rapidly, which now makes it possible to pursue the gold standard in public health, which is to slow down aging itself rather than just treat its consequences. Geroscience has come of age. It is the culmination of decades of research. It is not a theoretical construct. It has been demonstrated in the laboratory, that rate of aging can be modified in other species, which means rate control is possible in humans.

The first clinical trials of aging therapeutics, known as geroprotectors, are already underway, and the FDA is fully on board with this approach, which is to prevent disease by slowing aging. The health and economic benefits of geroscience will be substantial. A cure for cancer would be welcomed, but that's just one disease of many that plague older bodies, and a cure for cancer would only add about three years to life expectancy. A geroprotector will simultaneously lower the risk of all fatal and disabling diseases of aging simultaneously, which means even a modest effect would yield amplified health benefits. The cost savings in

healthcare alone would amount to over $38 trillion for each year of life generated with geroprotectors.

The primary goal of geroscience is the extension of healthspan, not lifespan. So these advances will not generate a fountain of youth in the colloquial sense, but it will fundamentally change what it means to grow old. We will remain younger longer, retain our youthful vigor for an extended period of time, and compress everything we don't like about aging into a shorter duration of time at the end of life.

There will be challenges that accompany the generation of a healthier and more robust older population, but the most precious commodity that we cherish most, our health, will be the gift of geroscience. It's difficult to imagine any scenario in the future where the generation of a larger healthy older population would not be pursued, even if challenges appear along the way.

This is just an introduction to geroscience, and I'd be happy to take any questions you may have. And thank you once again for the privilege of participating in this hearing. My written testimony will address all of these issues in far greater detail. Thank you very much.

[The prepared statement of Dr. Olshansky follows:]

SCHOOL OF PUBLIC HEALTH
UIC

September 16, 2022

Written testimony for the Subcommittee on Investigations and Oversight
"The Fountain of Youth? The Quest for Aging Therapies"
Date: Thursday, September 15, 2022
Time: 10:00 AM
2318 Rayburn House Office Building and online via zoom

S. Jay Olshansky, Ph.D.
School of Public Health, University of Illinois at Chicago
Board of Directors, American Federation for Aging Research

Thank you for the opportunity to participate in these important hearings on a new public health initiative known within the community of scientists and health professionals as Geroscience. The story I'm about to tell you is an easy one to communicate because all of us are experiencing aging firsthand.

In the modern era most people in developed nations – and a rising percentage of people in developing nations – have the privilege of living a long life; a privilege denied to most throughout history. Pioneers in public health, medicine, and science from just a few generations ago gave us the gift of a long life; and since then, humanity has worked hard to maintain this privilege and extend it to others less fortunate.

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The quest for aging therapies discussed in this hearing is at the heart of a new public health paradigm that has been in the works for the last half century, but which has gained traction just within the last few years. Here's the story in brief.

- Changes in our cells and tissues occur with the passage of time – we call it aging, but there is nothing magical about this since we see the same process occurring in our pets and automobiles.

Division of Epidemiology and Biostatistics
1603 W. Taylor St. (MC 923)
Chicago, IL 60612-4394

- It was suggested in the 50s, 60s, and 70s that aging should eventually become the target of medicine and science, but too little was known at the time about how aging happens.
- Medicine and public health did what it could in the interim to devise ways to detect and treat diseases; one at a time; as if independent of each other. This was a logical next step in dealing with the diseases that appear in aging bodies, but this approach came with limitations that can best be thought of as a game of whack-a-mole; knock one disease down and another appears shortly thereafter. The longer we live, the shorter the distance between diseases.
- The science behind the "how" question in aging has advanced rapidly, which now makes it possible to pursue the gold standard in public health, which is to slow down aging itself rather than just treat its consequences.
- Geroscience has come of age. It is the culmination of decades of research. It is not a theoretical construct – it has been demonstrated in the laboratory that rate of aging can be modified in other species; which means rate control is possible in humans; the first clinical trials of aging therapeutics (known as Geroprotectors) are already underway; and the FDA is fully onboard with this approach; that is, to prevent disease by slowing aging.
- The health and economic benefits of Geroscience will be substantial. A cure for cancer would be welcome, but that's just one disease of many that plague older bodies; and a cure for cancer would only add 3 years to life expectancy. A Geroprotector will simultaneously lower the risk of all fatal and disabling diseases of aging simultaneously, which means even a modest effect would yield amplified health benefits.
- The cost savings in health care alone would amount to over $38 trillion for each year of life generated with Geroprotectors.
- The primary goal of Geroscience is the extension of healthspan, not lifespan, so these advances will not generate a "fountain of youth" in the colloquial sense; but it will fundamentally change what it means to grow old. We will remain younger longer; retain our youthful vigor for an extended period of time; and compress everything we don't like about aging into a shorter duration of time at the end of life.
- There will be challenges that accompany the generation of a healthier and more robust older population, but the most precious commodity that many of us cherish most – our health – will be the gift of Geroscience.
- It is difficult to imagine any scenario in the future where the generation of a larger healthy older population would not be pursued – even if challenges appear along the way.
- This is just an introduction to Geroscience – I'll be happy to take any questions you might have and thank you once again for the privilege of participating in this hearing. My written testimony will address all of these issues in far greater detail.

1.0 Executive Summary

1.1 The First Longevity Revolution

In the 20th century humanity initiated one of the most important developments in the history of public health. We transitioned from a world in which a fourth, and sometimes a third of the babies born in a given year died before reaching their first birthday, to a time when over 81 percent of babies born will reach ages 65 and older; 38 percent will reach age 85; and more people will live to 100+ than at any time in history.[1] Life expectancy at birth rose by 30 years in just one century – a stark contrast from the slow rise during the previous several thousand years that was punctuated often by episodic communicable diseases that led to high mortality and drops in life expectancy.

While there have always been some people throughout history that survived to what we now think of as old age, it has been a relatively rare event. The longevity revolution experienced since 1900 means that public health and modern medicine achieved its collective goal of opening the door to adulthood and old age for most.

1.2 Declaring Victory in the Pursuit of Life Extension

There are still disparities in survival that exist among population subgroups who do not have the same access to old age enjoyed by others. Harmful risk factors such as obesity, smoking, drug use, lack of physical exercise and unequal access to health care and quality food, and income inequality, among other factors, means there is still room to improve public health along a broad range of fronts, and these efforts should continue. But the overall goal of saving children from dying in their first few years of life, and a high probability of surviving to older ages for most, has been accomplished.

1.3 The Emergence of Biological Aging as a Primary Risk Factor

Aging bodies exhibit common attributes associated with using these living machines beyond what I consider their biological warranty period.[2] Even if we adopt what might be thought of as ideal lifestyles, and if all disparities could hypothetically be eliminated, our bodies would still age, we would still grow old, and most deaths would occur between the ages of 65-95 from the same causes of death we see today.

When medical professionals and public health experts inform us, correctly of course, that many diseases are preventable through lifestyle modification, what they don't tell us is that death is a zero-sum game. Aging related fatal and non-fatal diseases and disorders are not eliminated

[1] https://mortality.org/

[2] http://www.sjayolshansky.com/sjo/Background_files/AmSci86-1998.pdf

through primary prevention – they are for the most part postponed and compressed into our remaining years of life.

If we are successful in reducing or eliminating one risk (such as smoking), we will no doubt reduce the risk of multiple diseases related to that risk, but biological aging marches on – uninfluenced by any progress made against specific diseases. Chronic age-related fatal and non-fatal diseases and disorders accumulate the older we get. This phenomenon is known as competing risks, and it is the reason why the life expectancy of national populations will not likely exceed about 85-88 years for men and women combined under present conditions.[3]

1.4 Rising Prevalence of Aging Related Conditions is a Product of Success, not Failure

The modern dramatic rise in the prevalence of heart disease, cancer, stroke, Alzheimer's disease, osteoporosis, arthritis, vision and hearing impairments, etc. – are a product of success – not failure. We have to live long enough for these diseases to be expressed. The first longevity revolution in the 20th century accomplished its goal of redistributing death from the young to the old, but our longevity revolution came with a price[4] – a Faustian bargain that exchanged longer lives for the diseases of aging.[5]

This longevity revolution made visible the diseases of aging. This means that the underlying biological processes of aging that give rise to these diseases, has become the most important risk factor for their emergence and severity. While behavioral and inherited risk factors still play a role in the onset and severity of the diseases of aging, they would still occur in us all even if optimal behavioral risk factors were adopted and all disparities eliminated.

Extended survival in the modern era has therefore presented itself as a unique public health dilemma never before experienced by humanity.[6] In the last 50 years modern medicine has achieved great success in detecting and treating the diseases of aging; personalized medicine is advancing rapidly; genomics opens the door to hyper-personalized medical interventions; and reductions in health disparities and improved behavioral risk factors are at least theoretically achievable; but none of these advances in public health currently have or will have any influence on the underlying biological processes of aging that give rise to diseases common in old age. The aging of our bodies is uninfluenced by any of these achievements, and it is this dilemma that is being addressed by the emergence of Geroscience.

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[3] http://www.eurohex.eu/bibliography/pdf/1297018782/Olshansky_1990_Science.pdf

[4] http://www.sjayolshansky.com/sjo/Background_files/PROJECT%20M_JAY.pdf

[5] https://europepmc.org/article/med/29238709 [click on "open pdf"]

[6] https://www.researchgate.net/profile/S-Olshansky/publication/274167075_The_Longevity_Dividend/links/5ba791e445851574f7e01e1e/The-Longevity-Dividend.pdf

1.5 The Emergence of Geroscience[7]

It was believed until recently that the aging of living things was immutable – an inevitable byproduct of extended survival. It has since been discovered that there can be no aging or death programs built into our genome that leads to programmed obsolescence; the rate of biological aging varies dramatically between individuals (e.g., biological time varies between individuals while clock time is constant); evidence has emerged demonstrating that biological aging in humans and other species is inherently modifiable; and importantly, the first clinical trials testing potential therapeutic aging interventions are already underway.[8,9,10]

Delayed aging through a variety of interventions has already been accomplished in other species by scientists working in Geroscience. Given the common theme of how selection operates across species, there is abundant evidence that aging modification is possible in humans.[11]

These discoveries about aging have now made it possible to formulate and deploy an entirely new approach to public health known as Geroscience. *The premise is straightforward. Instead of preventing or treating each fatal and disabling disease of aging as if it had an independent etiology and progression, Geroscience targets all of them at the same time – with a single intervention.* Indeed, it's possible to have more than one "single intervention" – but each Geroprotector would be expected to have a systemic effect on all aging systems in the body. Given the absence of aging or death programs driven by our genes, this means that multiple Geroscience-developed therapeutics are possible. Scientists involved in advocating for Geroscience are acutely aware of the broad range of potential therapies, and they're aggressively pursuing all of them at the same time.

I have referred to the importance of Geroscience to the modern era of public health as Primary Prevention with A Capital P.[12] Medicine and public health professionals have been advocating for primary prevention for decades – the end result of which is well-established improvements

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[7] https://www.afar.org/imported/fall2013ppar.pdf [the entire issue of Public Policy & Aging Report is devoted to explaining the origins of Geroscience]

[8] https://www.amazon.com/Aging-Longevity-Dividend-Collection-Perspectives/dp/1621820807/ref=sr_1_1?crid=11WJZ2LNR4JL1&keywords=aging+the+longevity+dividend&qid=1663003179&sprefix=aging+the+longevity+dividend%2Caps%2C80&sr=8-1&ufe=app_do%3Aamzn1.fos.006c50ae-5d4c-4777-9bc0-4513d670b6bc

[9] https://www.researchgate.net/profile/Julia-Rowland-2/publication/262386365_Advances_in_Geroscience_Impact_on_Healthspan_and_Chronic_Disease/links/548f1c910cf225bf66a7fb95/Advances-in-Geroscience-Impact-on-Healthspan-and-Chronic-Disease.pdf

[10] https://books.apple.com/us/book/a-measured-breath-of-life/id604410007

[11] https://link.springer.com/book/10.1007/978-3-319-23246-1

[12] https://www.researchgate.net/profile/S-Olshansky/publication/274167075_The_Longevity_Dividend/links/5ba791e445851574f7e01e1e/The-Longevity-Dividend.pdf

in ***healthspan*** (the number and proportion of the years of life spent in good health). As such, foundational support for Geroscience was spawned in the early 20th century as the detection and prevention of disease has always been the gold standard of how public health operates most efficiently.

Geroscience and the therapeutic interventions being pursued should therefore best be thought of as highly efficient methods of accomplishing what modern medicine is already trying to achieve – good health at every age. Geroscience will achieve this end with far greater efficiency because a single intervention will target multiple disease endpoints – simultaneously.

It has been suggested that healthy life experienced by older people might be one of the most precious commodities that exist.[13] I contend that healthspan has always been the primary goal of medicine and public health.

This combined body of knowledge has led researchers in the field of aging and a broad range of health professionals from physicians to health economists, to propose a new paradigm in public health designed specifically to address the modern dilemma of a rising prevalence of aging related diseases. I have explained the entire concept of Geroscience using just 300 words.[14]

1.6 What Might Happen to Public Health in the Absence of Geroscience?

It has been suggested that in the absence of Geroscience and an effective therapeutic, it's possible that the current model of treating diseases one-at-a-time as if independent of each other, could lead to rapid increases in chronic disease prevalence in the coming decades.[15] Disease management in an aging world without Geroscience, then becomes an ever more rapid game of whack-a-mole where each disease knocked down independently, leads to multiple other aging related diseases popping up shortly thereafter.

Aging and life extension without Geroscience could lead to a dramatically rising prevalence of aging related conditions.[16] We should then expect escalating health care costs associated with detecting and treating multiple aging related diseases that appear closer together in the last decades of life.

1.7 What is The Goal of Geroscience

To extend healthspan by compressing the frailty and disability that comes with aging, into a shorter duration of time near the end of life. What would a successful Geroscience therapeutic do for us? The life and death of Queen Elizabeth II is an exemplar of what Geroscience is pursuing – a healthy active life with a short period of frailty at life's end. Conceptually, think of

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[13] https://academic.oup.com/gerontologist/article/56/Suppl_2/S167/2605367

[14] https://www.dropbox.com/s/en3zn6b8y0ghohb/300%20WORDS.mov?dl=0

[15] https://journals.sagepub.com/doi/abs/10.1177/089826439100300205

[16] https://www.frontiersin.org/articles/10.3389/fmed.2017.00215/full [click on "download article"]

it taking 80 years of clock time to become biologically 60-year-old; or 90 years of clock time to become biologically age 70. Extending healthspan is the primary goal, and the cost savings associated with a successful Geroprotector that yields just a one-year increase in life expectancy would be $38 trillion.[17,18] **Geroprotectors are not the "fountain of youth"; but they will fundamentally change what it means to grow old.**

[17] https://www.escueladepensamiento.org/wp-content/uploads/2021/08/s43587-021-00080-0.pdf

[18] https://www.proquest.com/openview/88e55a15d518b155e010620da1e0b3cb/1?pq-origsite=gscholar&cbl=4365298

2.0 Common Questions and Challenges to Geroscience

2.1 Will Geroscience be the Fountain of Youth?

No. If the concept of a fountain of youth is taken in its literal sense as that presented in the popular literature where we become younger versions of ourselves by using some intervention, this is not going to happen in my view. There are many instances of exaggeration and embellishment among some in the scientific and medical community regarding the use of this phrase – some of which is driven by those seeking to profit from these therapies or research dollars from investors – but most researchers in the field stay away from mentioning "fountain of youth" in the same sentence as Geroscience.

Reversing some of the signs and symptoms of aging and lowering the risk of death and frailty is already possible with the use of diet, exercise, and risk factor modification – but there are limits to how much these kinds of interventions can influence lifespan and healthspan.

If "fountain of youth" is interpreted to mean that we can alter the age trajectory of mortality and disability through scientific means that have been properly tested for safety and efficacy, then under these conditions the phrase may be appropriate.

Those of us involved in Geroscience are acutely aware of a long history of hucksterism that has followed medicine and public health for thousands of years,[19] so most shy away from using this phrase. I personally avoid using this phrase, just as I avoid the phrases "age reversal" and "immortality".

I view Geroscience as the next logical paradigm in public health that will simultaneously avoid the dangers of life extension brought forth by treating one disease at a time and enhance the probability that healthspan will be extended and morbidity and disability compressed.

2.2 If We Delay Aging, Aren't We Just Pushing the Same Health Challenges to Later Ages?

The focus of Geroscience is healthspan extension, not lifespan extension. I've referred to the time period later in life when frailty and disability rise exponentially as the "Red Zone."[20] The first longevity revolution enabled large segments of every birth cohort in the last few generations to live into older ages, but the price paid for this success is a rising prevalence of diseases expressed in this period of the lifespan.

The current medical model is designed to push even more people into the Red Zone one disease at a time. By contrast, the focus of Geroscience is to compress the Red Zone, not extend life. As

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[19] https://books.google.com/books?hl=en&lr=&id=LM00AwAAQBAJ&oi=fnd&pg=PP1&ots=NPN2d_tbaa&sig=Ib6fid2BVLyjnfbpJ4KwqA1hCjk#v=onepage&q&f=false

[20] https://jamanetwork.com/journals/jama/article-abstract/2703114

such, Geroprotectors are expected to generate fewer years of frailty and disability for each successive generation.

Health challenges associated with survival into later ages would therefore be delayed **and** compressed rather than just postponed. Geroscience is being developed for the combined effect of healthspan extension and disease compression.

2.3 Would Extended Healthspan Reduce Future Healthcare Spending?

Rather than using my own words here, I'm going to include the abstract to an article recently published that explains how much health care costs would be reduced through the use of a Geroprotector.[21]

> "Developments in life expectancy and the growing emphasis on biological and 'healthy' aging raise a number of important questions for health scientists and economists alike. Is it preferable to make lives healthier by compressing morbidity, or longer by extending life? What are the gains from targeting aging itself compared to efforts to eradicate specific diseases? Here we analyze existing data to evaluate the economic value of increases in life expectancy, improvements in health and treatments that target aging. We show that a compression of morbidity that improves health is more valuable than further increases in life expectancy, and that targeting aging offers potentially larger economic gains than eradicating individual diseases. We show that a slowdown in aging that increases life expectancy by 1 year is worth US$38 trillion, and by 10 years, US$367 trillion. Ultimately, the more progress that is made in improving how we age, the greater the value of further improvements."

2.4 Would Extended Healthspan Create Challenges for Age Entitlement Programs?

The number of healthy older people would rise in this century with the dissemination of Geroprotectors, creating challenges for age entitlement programs such as Social Security and Medicare, although per capita medical costs would decline.[22] Exhibit 4 in this reference indicates the magnitude of the financial challenge, but the authors argue that adjusting the eligibility ages for these programs would address the challenge. A quote from that article appears below where this issue is addressed head on:

> "Given the large social return, the question then becomes how we could accommodate these changes fiscally. Several policy measures might achieve fiscal balance—we demonstrate one involving eligibility changes—but a full evaluation of the options is beyond the scope of this research. However, we note here one benefit of delayed aging that might enlarge the set of possibilities: With people staying healthy until a much later age, it might be more feasible to justify raising the eligibility age for public programs for seniors. Arguments against doing so often note that life

[21] https://www.escueladepensamiento.org/wp-content/uploads/2021/08/s43587-021-00080-0.pdf

[22] https://commed.vcu.edu/Chronic_Disease/aging/2014/delayingaging.pdf

expectancy increases in lower socioeconomic groups have lagged far behind those in better-off groups. A future in which delayed aging increased the health of all socioeconomic groups would make these increases in eligibility ages more palatable."

2.5 Is Geroscience a Form of Enhanced Primary Prevention – An Approach to Aging Related Diseases that is Already Accepted and Advocated Across the Globe?

Yes. If health promotion and disease prevention is the mantra of medicine and public health, then Geroprotectors represent an enhanced or amplified version of desirable interventions that help us deal with aging bodies and minds.

However, instead of treating health conditions as they arise (again, the concept of competing risks linked to modern medicine), Geroprotectors are designed to postpone the need for all health interventions at once. If is it desirable to avoid taking statins or medications to treat diabetes or repair worn out knees and hips or avoid cancer treatments or cardiovascular interventions, then Geroprotectors offer the most comprehensive method of achieving these goals.

2.6 Is it Selfish for Long-Lived Countries to Seek Aging Interventions when Other Countries Still Suffer from Communicable Diseases?

No. Just because different countries are on different health and longevity trajectories, does not mean those already able to survive to later ages, should wait until all other countries catch up before seeking out more efficient ways to combat disease. Besides, ongoing efforts to combat communicable diseases in developing nations are designed specifically to enable larger segments of these populations to live long enough to experience aging. Keep in mind that older individuals with aging related health conditions exist in all nations, regardless of whether they have a lower life expectancy than average. All nations – developed and developing alike – will benefit from the development of Geroprotectors. There is also reason to believe that disadvantaged subgroups of the population that suffer from chronic age-related diseases may benefit more from Geroprotectors given their higher risks to begin with.

2.7 When Should we Expect Physicians to Prescribe a Safe Geroprotector?

No one can know the answer to this question. What we do know is that Phase I clinical trials are already underway to test one or more Geroprotectors in humans – so this is no longer a hypothetical exercise. If the level of funding for Geroscience ramps up as expected, we can anticipate accelerated results from these clinical trials. I'm optimistic enough to suggest that most people alive today will be using one or more Geroprotectors in their lifetime, and they will be presented to the public as treatments for specific diseases – with the suggestion that their influence could extend to multiple disease endpoints. Metformin is a good example. While Metformin is used to treat diabetes, it appears to have desirable side effect of lowering the risk of a range of fatal conditions, but the clinical trials have yet to start to test this hypothesis.

2.8 Will the FDA approve an intervention that targets aging?

Members of the scientific community met with the FDA in 2016 to discuss how clinical trials would need to be organized to test for and ensure safety and efficacy for the public when using Geroprotectors.[23,24] While the FDA normally operates by linking one treatment to one disease, they recognized the value in targeting multiple disease endpoints by modifying the biological aging processes and fully support this new paradigm of primary prevention. The FDA has been supportive of Geroscience by advising scientists on how to structure clinical trials to test for the safety and efficacy of Geroprotectors. The primary FDA goal of ensuring safety and efficacy would apply equally to the testing and use of Geroprotectors.

2.9 Will Geroprotectors be Safe?

Geroprotectors will need to go through clinical trials just like any other purported therapeutic intervention designed to treat health conditions. These interventions should not make their way into physician-advised treatment/prevention protocols until they're fully cleared by the FDA to be safe and efficacious.

Having said this, scientists in our field need to remain vigilant since it is a common practice for unscrupulous entrepreneurs to try and manufacture and sell aging interventions before the clinical trials are completed.

2.10 Can Geroscience Replace Diet, Exercise, and Risk Factor Control?

No. Taking a Geroprotector is not a license to adopt an unhealthy lifestyle. The same behavioral risk factors that shorten life and increase the risk of disease would be operational when using a Geroprotector.

Geroprotectors would likely enhance and extend to older ages the effectiveness of diet and exercise and risk factor control in extending healthspan and compressing morbidity and disability.

2.11 Would Geroscience Create Environmental Challenges?

I've heard comments like this over the years, but never understood the logic. If Geroprotectors yield more years of healthy life, I cannot think of a single condition in which the global environment would be challenged by such a desirable event. Perhaps population size would be marginally larger in the coming decades as death rates decline and frailty and disability are delayed and compressed, but the momentum for population growth is already built into the age structure of our species.[25] The additional person-years-of-life generated by Geroprotectors

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[23] https://www.dropbox.com/s/41enksum78r3l55/Clip%201.mov?dl=0

[24] https://www.dropbox.com/s/55htnsisaso4x1l/Clip2.mov?dl=0

[25] https://d1wqtxts1xzle7.cloudfront.net/49129129/The_aging_of_the_Human_Species20160926-30708-mb5jzd-libre.pdf?1474897147=&response-content-disposition=inline%3B+filename%3DThe_aging_of_the_Human_Species.pdf&Expires=1663013961&Signatu

would be noise compared to the population growth that is already destined to occur by mid-century.

2.12 Would Geroscience Accelerate Population Growth, Leading to Overpopulation?

No. As indicated, the momentum that will lead to a human population of about 9-10 billion by 2050 is an inevitable byproduct of past trends in fertility – referred to as momentum for population growth already built into the age structure. Even if death rates were to decline as a result of Geroprotectors, the effect on the growth rate of the population would be almost imperceptible.[26] Please keep in mind that Geroprotectors are not designed for life extension; they're designed to extend healthspan and compress frailty and disability. The link between Geroprotectors and global population growth is negligible.

2.13 Is Aging a Disease?

This is a point of contention in the field of aging. By declaring aging a disease, some believe it will be easier to get the FDA to approve targeted therapeutic interventions. Others, myself included, suggest that aging is no more of a disease than puberty or menopause – it is a natural developmental byproduct of operating our living machines long enough to witness its effects. Calling aging a disease implies that all older people are, by definition, diseased – which is an example of ageism. We're not against aging or growing older – which is what the 'aging disease' designation implies by default. What we are seeking to achieve is an extension of the period of healthy life. Declaring aging a disease is just not necessary to launch this new movement in public health.

Besides, the FDA has already approved Geroprotectors to target multiple disease endpoints all at once, without declaring aging a disease.

2.14 Does Geroscience Intervene in God's Will?

Some critics suggest that the fundamental goal of Geroscience is to tamper with mother nature or god's will, and that we should not be pursing such efforts. But virtually all of public health is designed to tamper with our external and internal environments in one way or another to seek out ways to allow our bodies and minds to operate more efficiently and with less disease. For example, dentistry taught us how to make our teeth last longer; vaccinations are designed to use the body's own defense mechanisms to combat communicable diseases; antibiotics enable us to combat bacterial infections that used to kill with regularity; diet and exercise are the body's equivalent of an oil, lube, and filter for your car (it's not required in either case, but we now

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[26] https://www.afar.org/imported/fall2013ppar.pdf [see Table 1 on p.5]

know that our cars and bodies operate more efficiently when done); surgical procedures that remove the gall bladder or appendix or the use of stents to treat cardiovascular disease or knee and hip replacements are all designed to combat "natural" bodily functions that are harmful; and the dissemination of medications as simple as aspirin or statins that are designed to help the body overcome immediate challenges – all together, among many other examples of "tampering" with how are bodies operate, represent forms of interfering with natural processes ongoing in the body. If one is critical of Geroscience, then they should not avail themselves of all of the other medical interventions described here that are designed to combat disease or treat and prevent the health challenges that come with extended survival.

Should someone not feel inclined to use Geroprotectors because it would violate their personal beliefs, they have the option to not use such interventions. Seventh Day Adventists adhere to this line of reasoning.

For those who wish to avail themselves of the tools of science and medicine to combat disease and extend healthspan, Geroscience will place into their physician's hands, what might be thought of as one of the most comprehensive tools ever developed by modern medicine to combat all of the diseases of aging simultaneously.

2.15 Are There Secondary Benefits Associated with a Successful Geroprotector?

If Geroprotectors had been available at the beginning of the Covid-19 pandemic, it would likely have dramatically reduced death and disability related to this communicable disease? Why? Because Covid-19 and other communicable diseases prey on subgroups of the population that are experiencing multiple health challenges (e.g., pre-existing conditions) – the very phenomenon of competing risks described earlier that explains why this virus tends to kill most effectively at older ages. The declining effectiveness of our immune system is one of the hallmarks of biological aging, so any intervention that delays the process of aging, will have secondary benefits associated with multiple infectious diseases including pneumonia and seasonal influenza, among others.

Geroprotectors will also likely be needed for astronauts that travel for extended periods in space due to high risks associated with exposure to radiation.

It is difficult to determine this far in advance what other attributes of human health might benefit from Geroprotectors, but it is safe to say that any intervention that enables us to slow down biological aging is likely to have as yet unforeseen benefits.

It is difficult to imagine any harm to human health that would follow from interventions that yield more healthy years of life.

Biography
S. Jay Olshansky

S. Jay Olshansky received his Ph.D. in Sociology at the University of Chicago in 1984. He is a Professor in the School of Public Health at the University of Illinois at Chicago, Research Associate at the Center on Aging at the University of Chicago and Chief Scientist at Lapetus Solutions, Inc. -- a company that he co-founded.

The focus of his research is on estimates of the upper limits to human longevity, exploring the health and public policy implications associated with individual and population aging, forecasts of the size, survival, and age structure of the population, pursuit of the scientific means to slow aging in people (*The Longevity Dividend*), and global implications of the re-emergence of infectious and parasitic diseases.

During the last thirty five years, Dr. Olshansky has been working with colleagues in the biological sciences to develop the modern "biodemographic paradigm" of mortality – an effort to understand the biological nature of the survival and dying out processes of living organisms. Dr. Olshansky is the first author of *The Quest for Immortality: Science at the Frontiers of Aging* (Norton, 2001); *A Measured Breath of Life* (2013); *The Rise of Generians* (2020); *Pursuing Wealthspan* (2020); and co-editor of *Aging: The Longevity Dividend* (Cold Spring Harbor Laboratory Press, 2015). His new book on the Longevity Dividend/Geroscience will be published with colleagues later this year.

Dr. Olshansky's recent work is focused on linking the scientific study of aging with investments in longevity and mortality related products. Dr. Olshansky is a Board member, American Federation of Aging Research (AFAR); he served on the Board of Scientific Advisors at PepsiCo; and he was co-chair of the Council on Aging at the World Economic Forum. In 2016, Dr. Olshansky was honored with the Donald P. Kent Award from the Gerontological Society of America, the Irving S. Wright Award from the American Federation for Aging Research, he was named a Next Avenue Influencer in Aging; and in 2017 he received the Alvar Svanborg Award. Dr. Olshansky received the Glenn Award from the Glenn Foundation for Medical Research in 2018.

Chairman FOSTER. Thank you. And next is Dr. Niedernhofer. Whoops, I think you're muted.

TESTIMONY OF DR. LAURA NIEDERNHOFER, DIRECTOR, INSTITUTE ON THE BIOLOGY OF AGING AND METABOLISM; MEDICAL DISCOVERY TEAM ON THE BIOLOGY OF AGING; PROFESSOR, DEPARTMENT OF BIOCHEMISTRY, MOLECULAR BIOLOGY AND BIOPHYSICS, UNIVERSITY OF MINNESOTA

Dr. NIEDERNHOFER. Good morning, and thank you very much for this opportunity to participate.

So geroscience refers to the fact that advanced chronologic age is the greatest risk factor for most diseases. Therefore, developing therapeutics that disrupt the biologic changes that universally occur with advanced chronologic age is not only logical, but potentially highly impactful to human health. A geroscience approach is anticipated to impact the health of the elderly to a greater extent than curing any single disease of old age, and this includes Alzheimer's disease or cancer. Importantly, geroscience aims to extend how long individuals are healthy, not how long they live, what we refer to as extending healthspan.

So geroscience is based on three facts. First, we are in an unprecedented period of human history in which the number of elderly is doubling and surpassing the number of young people. This establishes the need for a new approach to prevent our healthcare system from becoming overwhelmed and healthcare costs from skyrocketing. Second, the majority of people over the age of 65 have two or more chronic diseases. Hence, curing a single disease of old age will not dramatically improve the health of the elderly. Third, chronologic age contributes to the risk of most diseases to a much greater extent than other risk factors that we are currently treating. Thus, therapeutics targeting aging biology have the potential to be not only useful for many diverse diseases, but also to be highly effective at doing so compared to our current first-line treatments.

So today, geroscience is—where it stands is there is ample evidence that certain molecular and cellular events occur in most if not all people with advanced chronologic age. There's also ample evidence that some of these events can be therapeutically targeted in humans, as well as in disease models. We have in hand FDA-approved drugs that target and stop or even reverse these molecular and cellular events of aging biology. We also have extensive data from animal models, what we call preclinical data, demonstrating that geroscience-guided therapies prevent, attenuate, or even reverse age-related diseases, affecting most organ systems. This includes heart disease, Alzheimer's disease, and diabetes. There exists at least one drug mentioned, metformin, that appears to simultaneously stave off diabetes, heart disease, cancer, and cognitive impairment. There are also numerous other tentative geroscience drugs already approved by the FDA and in clinical use that should be tested for geroscience approaches. There's a lot of activity in the space of developing therapeutic interventions that target aging biology, primarily in academic centers at this point but gaining traction in the pharmaceutical industry.

So what I perceive as key barriers to progress are adequate funding to pursue geroscience research in a timely fashion, lack of physician scientists and infrastructure needed to support clinical trials in geriatric patients, lack of public knowledge about geroscience, and a lack of biomarkers that report how well an individual is aging relative to just using their chronological age, as we do now.

The Federal Government could facilitate geroscience research by providing Federal funding dedicated to supporting geroscience research across many disciplines; support for training physician scientists knowledgeable about clinical trials in geriatric patients; funding and support to create the infrastructure needed to advance geroscience research, including sharing of biospecimen and data; and facilitating the collection as well as the dissemination of information across diverse race, ethnic, and socioeconomic groups.

So what would be the societal implications? Well, although this is really not my area of expertise, I can offer my opinion. Aging biology affects virtually every aspect of how an individual interacts with their world, communication, transportation, housing needs, healthcare needs. The elderly exit the work force while requiring significantly more help. As a number of chronologically aged individuals continues to increase, we as a society will have to accommodate all of these changes. Geroscience, though, offers an alternative approach where we aim to keep those of advanced chronologic age healthy, independent, active, able to work if they choose, and able to contribute to the economy.

Given the wealth of scientific evidence supporting geroscience, I feel it would be irresponsible not to try this alternative. I personally cared for four parents and grandparents over the last few decades, each of whom had multiple diseases of old age, and I can attest it's time-consuming, costly, heartbreaking, but also robbing younger individuals of productively contributing to society.

Thank you very much.

[The prepared statement of Dr. Niedernhofer follows:]

Written Testimony on Geroscience from Dr. Laura Niedernhofer, MD, PhD September 15, 2022

Geroscience refers to the fact that advanced chronologic age is the greatest risk factor for most diseases. Therefore, developing therapeutics that disrupt the biologic changes that universally occur with advanced chronologic age is logical but also potentially highly impactful to human health.

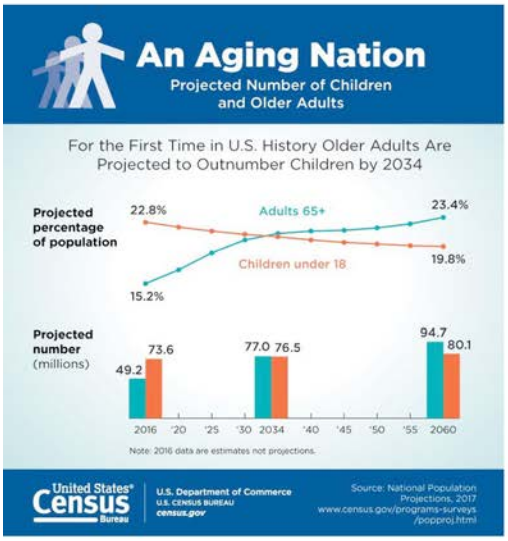
A Geroscience approach is anticipated to affect the health of the elderly to a greater extent than curing any single disease of old age, including curing Alzheimer's disease or cancer.

Importantly, Geroscience aims to extend how long individuals are healthy, not how long they live, what we refer to as extending *healthspan*.

Geroscience is based on three facts:

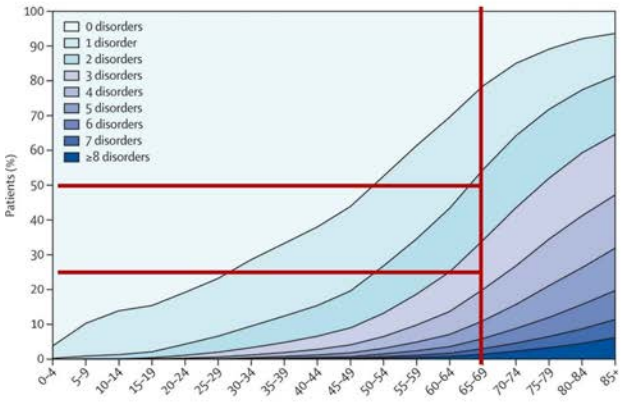
1) First, we are in an unprecedented period in human history in which the number of elderly is doubling and surpassing the number of young people. This establishes the need for a new approach to prevent our healthcare system from becoming overwhelmed and healthcare costs skyrocketing.

Our aging population:



2) Second, the *majority* of people over the age of 65 have two or more chronic diseases. Hence, curing a single disease of old age will not dramatically improve the health of the elderly.

Frequency of diseases by chronological age:



Diseases where chronologic age is the greatest risk factor:

- Osteoporosis
- Cardiovascular disease
- Neurodegenerative diseases
- Osteoarthritis
- Type II diabetes
- Cancer
- Macular degeneration
- Intervertebral disc degeneration

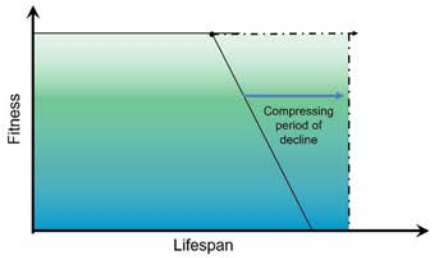
3) Third, chronologic age contributes to the risk of most diseases to a much greater extent than other risk factors that we are currently treating. Thus, therapeutics targeting aging biology have the potential to be not only useful for many diverse diseases but also highly effective at doing so compared to current first-line drugs.

Impact of chronic age on disease risk relative to other risk factors that we currently treat:

Geroscience-guided therapeutics are predicted to:

- Target multiple common chronic diseases
- Be more impactful on human health than treating other disease risk factors
- Be efficacious in most people because aging biology is largely universal
- Extend human healthspan not lifespan
- Reduce health care costs by ~$38T annually
- Not require de novo drug development and testing, reducing the time and cost before therapies are available

Goal of Geroscience:



Currently, where Geroscience stands today:

- There is ample evidence that certain molecular and cellular events occur in most if not all people with advanced chronologic age.
- There is also ample evidence that some of these events can be therapeutically targeted in humans and in disease models.
- We have in-hand FDA-approved drugs that target and stop or reverse these molecular and cellular events of aging biology.
- We also have extensive data from animal models (pre-clinical data) demonstrating that Geroscience-guided therapies prevent, attenuate, or reverse age-related diseases affecting most organ systems. This includes heart disease, Alzheimer's disease, and diabetes.
- There exists at least one drug that appears to simultaneously stave-off diabetes, heart disease, cancer, and cognitive impairment. There are also numerous other candidate Geroscience drugs already approved by the FDA and in clinical use.
- There is a lot of activity in terms of the development of therapeutic interventions that target aging biology, primarily in academic centers and gaining traction in the pharmaceutical industry.

Evidence for feasibility of targeting aging biology:

1) Centenarians illustrate that the human body is capable of being healthy late in life
    a. They experience 20+ years of disease-free life than the average person
    b. They spend <2.5-fold less on healthcare in the last 2 years of life than the average person
2) Diseases for which there is evidence that targeting aging biology is efficacious

- Alzheimer's disease and neuromuscular dysfunction
- Pulmonary fibrosis
- Non-alcoholic fatty liver disease, steatosis, and fibrosis
- Osteoporosis and osteoarthritis
- Kidney disease
- Coronary artery and cardiovascular disease
- Frailty
- COVID-19

Other conditions of accelerated aging in which patients stand to benefit from Geroscience therapies, in addition to the chronologically aged:

- Cancer survivors
- Chronic HIV patients
- Socioeconomic stress
- Astronauts
- Genetic diseases including Down's syndrome and Hutchinson Gilford Progeria

Existing FDA approved drugs that target multiple aspects of aging biology that are candidate Geroscience therapeutics:

- Metformin
- Rapamycin
- Acarbose
- Canagliflozin
- Aspirin
- Dasatinib
- Navitoclax
- Inhibitors of HSP90, SGLT2i, LSD1, angiotensin-converting enzyme or angiotensin receptor, BCL-2, tyrosine kinase, cardiac glycoside

Natural products available over-the-counter that are candidate Geroscience therapeutics:

- Quercetin
- Fisetin
- N-Acetyl Cysteine
- Piperlongumine
- Luteolin
- Curcumin

Other potential benefits of expansive Geroscience research:

- What is learned could be applied in organ transplantation to expand the number and age of organ donors and recipients.

- It is now clear that events across the entire human lifespan impact how we age. Understanding how will potentially benefit every person in this country.
- What is learned could be applied to extend the health of farm animals to improve productivity (eggs, milk, wool)

Key barriers to progress:

- Adequate funding to pursue Geroscience research in a timely fashion
- Lack of the physician scientists and infrastructure needed to support clinical trials in geriatrics
- Lack of public knowledge about Geroscience
- Lack of biomarkers that report how well an individual is aging better than their chronological age does

The federal government could facilitate Geroscience by providing:

- Federal funding dedicated to supporting Geroscience research across multiple disciplines
- Support for training of physician scientists knowledgeable about clinical trials in geriatric patients
- Funding and support to create the infrastructure needed to advance Geroscience research, including sharing of biospecimen and data.
- Facilitating both the collection and dissemination of information across diverse race, ethnic, and socioeconomic groups

Ethical and societal implications:

Although this is not my area of expertise, I can offer my opinion. Aging biology affects virtually every aspect of how an individual interacts with the world: communication, transportation, housing needs, healthcare needs. The elderly exit the workforce while requiring significantly more help. As the number of chronologically aged continues to increase, we as a society will have to accommodate all of this. Geroscience offers an alternative where we aim to keep those of advanced chronologic age healthy, independent, active, able to work if they choose, and able to contribute to the economy. Given the wealth of scientific evidence supporting Geroscience, it would be irresponsible not to try this alternative. I cared for four parents or grandparents over the last two decades each of whom had multiple co-morbidities and I can attest that it is time-consuming, costly, and heartbreaking.

BIOGRAPHY **Laura J. Niedernhofer, MD, PhD**

Laura Niedernhofer joined the University of Minnesota in July 2018 to direct the new Institute on the Biology of Aging & Metabolism and Medical Discovery Team on the Biology of Aging. She is a Professor in the Department of Biochemistry, Molecular Biology and Biophysics at UMN. Dr. Niedernhofer's expertise is in DNA damage and repair, genome instability disorders, cellular senescence, and aging biology. Her research program is centered on studying fundamental mechanisms of aging and developing therapeutics to target them. She contributed to the discovery of a new class of drugs called senolytics. Laura has served on study section for NCI, NIEHS, and NIA. She has been awarded for research in aging, cancer and environmental health science and was the 2018 recipient of the Vincent Cristafolo Rising Star in Aging Research awarded by the American Federation for Aging Research (AFAR). She is currently serving on the Advisory Council to the Division of Aging Biology at NIA and on the Board of Directors for American Federation of Aging Research. Laura was recently nominated to The Academy for Health and Lifespan Research.

Chairman FOSTER. Thank you. And as someone who shared the experience you just mentioned with his own parents, this is—it's an important thing to—so the aggregate quality of life of being a human.

And finally, we have Dr. Horvath.

TESTIMONY OF DR. STEVE HORVATH,
PRINCIPAL INVESTIGATOR, ALTOS LABS

Dr. HORVATH. Yes, my name is Steve Horvath. I'm testifying in my personal capacity as a scientist. I'm very honored to speak to the Members of this Committee today.

I would like to speak to you about a new class of molecular biomarkers known as epigenetic clocks, which allow us to measure aging in all mammalian cells, tissues, and organs. Epi means above, and it relates to how epigenetics or methylation controls which genes are turned on or off. Building on work following the Human Genome Project, we now understand that your DNA alone is not your destiny. Epigenetics can drive change in your cells. And importantly, it is believed that many of these epigenetic changes may be modifiable. Many researchers believe that emerging work in epigenetics may be critical for the development of more personalized medicines.

An epigenetic clock is a biochemical test that is based on DNA methylation, which are chemical modifications of the DNA molecule. We now can reliably measure human age using a simple blood draw. By applying epigenetic clocks to DNA collected before and after a drug treatment, we're able to quickly determine if a drug is affecting the epigenetic aging process. Using these epigenetic clocks, we and others have found interventions that greatly reversed age of mice and rats. Some of these results are expected to matter for human health as well.

In 2019, Greg Fahy and I published results from a phase 1 human clinical trial that demonstrated a notable first, that a treatment consisting of already-approved drugs and supplements could reverse all established epigenetic clocks in healthy older men aged between 50 and 65. In a current phase 2 trial known as TRIIM-X, which is going on in California right now, we will assess if this same treatment can be applied to women and men between 40 and 80. The trial may also determine if the treatment leads to functional improvements in older individuals such as increased leg strength that will delay onset of frailty.

This ongoing work has provided a helpful template for the longevity research community. When used along with standard clinical and physiological testing, epigenetic clocks could add a rigorous and practical approach for determining if a new longevity drug is effective for use in healthy, older individuals. Preventative medicine trials that previously took many years may now be completed in only one to two years, although tracking of longer-term health outcomes will be critical as well.

The biotech industry is also now developing exciting new drugs targeting the biology of aging. As the data mature, there will be a need for a clear regulatory framework for drug approval in healthy, older individuals. In addition, looking at current disease classifications to ensure they are inclusive of these new therapies would be

very helpful. My hope is that this Committee and others in government will recognize the recent biomedical breakthroughs, including biomarkers of aging, and modernize the approval process for new longevity treatments. We have an opportunity and arguably an obligation to leverage these recent biomedical breakthroughs to identify interventions that may delay the onset of chronic diseases and which may revolutionize the field of preventative medicine.

When we look back at past centuries, we find the high rate of child mortality completely unacceptable. Nearly 50 percent of babies born in the U.S. in 1800 did not live past their fifth birthday. I predict that future generations will look back at our times and recoil in horror at the high mortality rate in the elderly. Globally, over 100,000 people die each day due to age-related diseases. We don't have to accept this anymore.

Thank you for your time and invitation to speak to you.

[The prepared statement of Dr. Horvath follows:]

Written Testimony of Steve Horvath
Hearing on "The Fountain of Youth? The Quest for Aging Therapies"
House Committee on Science, Space, and Technology
Subcommittee on Investigations & Oversight
September 15, 2022

My name is Steve Horvath. I was a professor of Human Genetics and Biostatistics at the University of California, Los Angeles ("UCLA"). My research lies at the intersection of several fields including biogerontology, anti-aging clinical trials, epigenetic biomarkers of aging, epidemiology, systems biology, and comparative biology. With my UCLA colleagues, we published the first epigenetic clock for saliva, the first pan-tissue clock, and the first pan mammalian clock. I've recently joined Altos Labs, a biotechnology start-up focused on cellular health and rejuvenation.

I am testifying in my personal capacity as a scientist and researcher and am honored to speak to the members of this committee on the timely and important topic.

Epigenetic Clocks in Aging Studies

I am here today to speak to you about a new class of molecular aging biomarkers known as epigenetic clocks, which allow us to measure aging in all mammalian cells, tissues, organs.

Epigenetic aging clocks keep track of chemical modifications of the DNA molecules. An epigenetic clock is a biochemical test that can be used to measure the age of a cell. The test is based on DNA methylation levels, measuring the age-related changes to the methyl groups to one's DNA molecules in your genome.

"Epi-" means "above", and it relates to how epigenetics, or methylation, controls your gene expression. Building on work following the Human

Genome Project, we now understand that your DNA or genome alone is not your destiny. Epigenetics much more than genetics alone can drive change in your cells and tissues, and importantly it is believed that many of these epigenetic changes may be modifiable. Many researchers believe that emerging work in epigenetics may be critical for development of more personalized and effective medicines.

We now can reliably predict human age currently using a simple blood draw. By applying epigenetic clocks to DNA collected before and after a drug treatment, we're able to quickly determine if a drug is affecting the aging process. Using these epigenetic aging clocks, we and others have found interventions that greatly reverse the age of rodents. Some of these results are expected to matter for human health as well.

In 2019, we published results from a Phase 1 human clinical trial that demonstrated a notable first – that a treatment consisting of already approved drugs and supplements could reverse all established epigenetic clocks in healthy older men age 50 to 65. This work was sponsored by a start-up biotechnology company named Intervene Immune. A Phase 2 trial known as TRIIM-X is now ongoing in California in order to assess if this same treatment can be applied to older men & women age 40 to 80. The trial may also determine if it leads to functional improvements in older individuals, such as increased leg strength that will delay onset of frailty.

This ongoing work has provided a very helpful example or template for the longevity research community. When used along with standard clinical and physiological testing, epigenetic clocks could add a rigorous and practical approach for determining if a new longevity drug is safe & effective for use in healthy older individuals. Preventative medicine trials that previously took 5-7 years may now be completed in only 1-2, although tracking of longer-term health outcomes is critical as well.

The biotech industry is also now developing exciting new drugs targeting the biology of aging. As the data mature, there will be a need for a clear

regulatory framework for drug approval in healthy older individuals. In addition, looking at current classifications to ensure they are inclusive of these new therapies would be helpful.

My hope is that this Committee and others in government will recognize the recent biomedical breakthroughs including biomarkers of aging and modernize the approval process for new longevity treatments.

When we look back at past centuries to find the high rate of child mortality completely unacceptable: nearly 50 percent of babies born in the US in 1800 did not live past their fifth birthday. I predict that future generations will look back at our times and recoil in horror at the high mortality rate and our poor public health. Globally, over 100,000 people die each day due to age-related diseases. We don't have to accept this anymore.

We have an opportunity and arguably obligation to leverage recent biomedical breakthroughs to identify longevity interventions that may delay the onset of chronic diseases, and which may revolutionize the field of preventative medicine.

Thank you for your time and invitation to speak on this important topic.

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Short narrative biography
Steve Horvath

Dr. Horvath is a biogerontologist, whose research lies at the intersection of several fields including epigenetic biomarkers of aging, preclinical and clinical studies, genomics, epidemiology. Dr Horvath is a principal investigator at Altos Labs. He is a tenured full professor in Human Genetics and Biostatistics at the University of California, Los Angeles.

Horvath and his UCLA colleagues published the first epigenetic clock for saliva in 2011. In 2013, he published the first pan-tissue clock, also known as the Horvath clock. Recently, he presented a universal clock that measures age in all mammalian species.

The recipient of several awards, he has been on Clarivate's annual list of the world's most influential scientific researchers every year since 2018.

Dr Horvath received a Ph.D. in Mathematics from the University of North Carolina, Chapel Hill in 1995 and a Doctorate of Science in Biostatistics from the Harvard School of Public Health in 2000. Dr Horvath is a US citizen who grew up in Frankfurt, Germany.

Chairman FOSTER. Thank you. And at this point, we will now begin our first round of questions, and the Chair will recognize himself for five minutes.

Dr. Niedernhofer, there seem to be at least three active subfields of research here. There's cellular senescence, cell reprogramming, and thymic rejuvenation. There are probably others. Could you please briefly explain a bit about the status and goals of each of these and other approaches, beginning with senescent cells if you—since you're one of the experts on that? And might you shoot for three minutes?

Dr. NIEDERNHOFER. Well, thank you very much for this question. What the field has done, it has recognized what we call hallmarks of aging. So these are sort of the universal processes that seem to happen in every organism from worm models to rodents, primates, humans. And these are all candidate targets for therapeutics. Senescent cells have emerged as one of those targets or hallmarks of aging that is very, very tractable, so this allows us to develop therapeutic drugs that target senescent cells.

The reason this is important is senescent cells are cells that are stressed, they've responded to that stress in our body, which is a very healthy thing to do. It suppresses cancer, but afterwards, the cells linger chronically and they secrete things into their environment, which are very proinflammatory. And it's quite clear that senescent cells at this point promote aging, as well as contribute to virtually every age-related disease. And so if we can clear them with drugs, help the body and the immune system clear them, we really see a tremendous impact of this approach.

Reprogramming is a little bit different, where you're trying to rejuvenate through epigenetic changes, as Dr. Horvath has spoken about, to rejuvenate the cells rather than get rid of damaged cells. So this holds a lot of promise as well.

There's lots of other approaches, rejuvenating stem cells, improving the response to genome instability, nutritional stress, and the response to nutrients. So we have lots of different opportunities here to target biology of aging, and I think they're all coming together quite nicely.

A very important point to make is all of these hallmarks of aging are truly interrelated, meaning if we target any one of them, we can actually improve multiple of these hallmarks of aging and literally remove damaged cells or rejuvenate existing ones. And so there's a lot of promise here. Thank you.

Chairman FOSTER. Thank you. And, yes, I was struck by a study that you co-authored where healthy adult mice were dosed with extra senescent cells. And so can you just describe quickly what was the result of the senescent cells?

Dr. NIEDERNHOFER. Yes, that's a great question. So what's really important to prove cause and effect, which has been extremely challenging in the field of biology of aging, we have these hallmarks of aging, but do they really cause aging? So what you have to do is add senescent cells if you want to test the hypothesis that they drive aging, or take them away. And so we have dosed animals with extra burdens of senescent cells, and the impact on those animals are they have reduced spontaneous activity, reduced grip, and altered metabolism. So all of the things that we observe with

normal aging is—can be driven by the transplantation of senescent cells into a model organism. And in fact, one of our studies showed that senescent immune cells are one of the most potent ways to drive aging of all of the tissues in your body.

So we also have very strong pharmacologic as well as genetic evidence that if you remove senescent cells, you can regain the spontaneous activity, the grip strength, the endurance, so all of these things that we really are passionate about and lose as we become more frail with old age.

Chairman FOSTER. Yes, thank you. And I find these senescent cells fascinating, just the—you know, the concept that there are these cells, they're not dead yet, but they're not doing their job. You know, until recently, it actually reminded me very much of the U.S. Senate. But it's not the subject of this hearing.

Anyway, well, let's see. I guess I am close enough to the end of my time, and I'll turn it over to the Ranking Member.

Mr. OBERNOLTE. I'll second the sentiment about the Senate.

Thank you very much to our witnesses. It's been a really interesting hearing.

Dr. Olshansky, I'd like to start with you. I was very interested in both your oral and written testimony where you talked about the potential cost savings of $38 trillion a year per year of extended lifespan? Could you talk a little bit about in that analysis how you came up with that number?

Dr. OLSHANSKY. Actually, I didn't come up with that number. That was research that was done by some of our colleagues in the UK, some scientists at Harvard. That's a much longer story that I'm—and I'm not the expert on having come up with the $38 trillion estimate. So I'm actually going to leave that question to the scientists that generated that research, but I'd be happy to send the citation or provide that citation to anyone who wants it. But——

Mr. OBERNOLTE. OK, well, let's talk about the potential other side of that equation, which, you know, you talked about how currently that dealing with aging is like playing Whac-a-Mole and that perhaps one of the—in your written testimony, you said perhaps one of the breakthroughs in geroscience would be disease compression where, you know, we're compressing the period of our lives that we're experiencing these. But, you know, what if it's somewhere in the middle where we're just—we just get really good at whacking the moles right as we move along. And—but in that case, you would actually achieve a greater human lifespan but at much greater cost. And actually, I mean, that's kind of what we've been experiencing so far with our—our healthcare system, right? This is—as a society, we've been really grappling with this issue of how to equitably distribute those costs because it's great that we have these greater lifespans, but you know, the treatments are becoming increasingly more expensive. So you know, what—why is—let me ask you to defend why you think it's a cost savings and not an increased cost, you know, given the fact that either one would be preferable to what we've got now?

Dr. OLSHANSKY. Yes, so, several years ago, in 2018, I published an article in the *Journal of the American Medical Association* entitled "From Lifespan to Healthspan." And in there, I describe what

we've done to ourselves. We basically in the 20th century redistributed death from the young to the old. We've extended survival very effectively past the ages of 65 and 85. But we've done it against the backdrop of one of frailty and disability that rises exponentially with chronological age. I refer to that as the red zone, a time period where if you live into this red zone, frailty and disability is extremely high.

If we continue along the pathway of attacking one disease at a time, in all likelihood, we will succeed in extending survival deeper and deeper into the red zone, which would raise costs per capita, would raise overall costs associated with healthcare. There would be a pretty heavy price to pay if we continue along the current path.

The focus of geroscience is not on the line that pushes us toward later ages. It's on the red zone itself. It's to compress the red zone, push it to later ages so that when bad things happen that are associated with aging, they happen over a much shorter time period. And all the costs associated with that—with end-of-life care and end-of-life health issues would be less costly and compressed over a shorter time period. And that is the kind of thing that we're seeing in the animal models is compression of morbidity, not just lifespan extension.

Mr. OBERNOLTE. Thank you. Dr. Niedernhofer, I had a question for you. I thought it was really interesting when you were talking about the societal implications of a greater lifespan. And you were careful to say this isn't your field of expertise, but I'm wondering your thoughts on—on some of the negative consequences. Because if you take the limiting case where human lifespan is greatly extended, then you get into a situation where every single birth adds to the population of the planet. So, I mean, what are the ethical implications of that? Because that would seem to be something that also society would struggle to deal with?

Dr. NIEDERNHOFER. It's a great question, but I would really like to emphasize that our goal is to make the elderly more healthy, making them more useful so they're able to work, contribute, spend their money, vacation, do all those things that we really enjoy. So I don't see a negative consequence of this. Keeping people healthy, active, more useful I think is all good for the economy. But I am not an expert.

Mr. OBERNOLTE. Sure. Well, I mean, it's—obviously, this is something that we should do it need to do. But, I mean, we also need to be realistic about the societal implications of it. All right. Well, thank you very much. I see my time is expired. I yield back, Mr. Chairman.

Chairman FOSTER. Thank you. And we will now recognize Representative Perlmutter for five minutes.

Mr. PERLMUTTER. Thanks, Mr. Chair. And this—maybe as I'm getting older, this is a very fascinating hearing we're having today. And I—you know, we just had to move my mom into memory care.

So, Dr. Horvath, I want to start with you. In terms of your biomarkers and your ability—the ability that's being developed to look at things across the board, so cardiovascular or cancer or, you know, brain diseases, so as somebody develops Alzheimer's, I mean, how—are you seeing things that might help us reverse something

like that? Because going back to Mr. Obernolte's questions, we see sort of on a macro basis just huge cost to society, particularly from Alzheimer's. So can you sort of respond to that for me?

Dr. HORVATH. Yes. When it comes to Alzheimer's disease, I do see exciting results, certainly in basic research. I'm just at a conference here, and I see wonderful, very promising talks. We really understand a lot about Alzheimer's disease. As our knowledge increases, we will undoubtedly develop effective medicines. I'm just as sure as you can be. The question is how fast. There is always a chance of serendipity, you know, but I'm very happy to hear that there are ongoing clinical trials.

And what I can tell you, Alzheimer's disease, of course, it's to—protein aggregation, so called proteostasis, but also many other facets of aging that touch it, the immune system, also epigenetic changes, changes in garbage removal, autophagy in the cells. And so—and there's really an army of researchers working on it, on all of these facets. And the same of course pertains to other diseases.

Mr. PERLMUTTER. So the other panelist is saying, look, if we are able to, through geroscience, start affecting how cells age, I assume that this would, you know, as a general principle, help slow down the potential for an Alzheimer's or that kind of disease? I mean, are you seeing that in your research?

Dr. HORVATH. Yes. The idea is make cells more resilient. Young cells are resilient. They can tolerate various forms of stress. And so, yes, I think that's a very promising avenue.

Mr. PERLMUTTER. Thank you. I'd like to—you know, our problem as legislators is to figure out what are going to be the macro results of this, you know, what are the consequences? And, Dr. Niedernhofer, you started to opine on that a little bit. I mean, I think the good news is if we're successful here—you know, I'm—I think you're probably right that we would have independent, productive, you know, happy people. You know, and that's my goal as a legislator, to improve society. So kind of give us what you think might be some of the problems that we as legislators would face if you as doctors and scientists are successful.

Dr. NIEDERNHOFER. Problems that we would face? I think it would help solve a lot of problems. I mean, one example I'd like to give to you is think about centenarians. So it's a fact that they experienced 20-plus years of healthy living. And in the last two and a half years of their life, they use the healthcare system much less. They're not sick, they're not going to doctors, they're not taking as many medicines. And so biology tells us we can be fit, healthy, less frail in old age. Picture Queen Elizabeth. I think she was a beautiful example. She's working, she's on vacation, and then she just has this very compressed period of morbidity. So I look at this as an opportunity to solve problems.

Mr. PERLMUTTER. Thank you. I'll yield back to the Chair. I think we'll get to do a second round, so I just need to digest all of this that you people are talking about. We—I would say one thing. We had a Governor in Colorado, Dick Lamm, who was called Governor Gloom, some of you may remember, because he said everybody had a duty to die and so that we didn't put extra pressure and costly pressure on the healthcare system. And you're saying that if this

is successful, we're going to do just the opposite, so I appreciate that. I yield back to the Chair.

Chairman FOSTER. Thank you. And we'll now—let's see. Is Representative Beyer still on the call? He was due up next, but if—he is apparently not here. All right. In that case, I think we'll start our second round.

You know, and so—let's—I was caught a little bit unawares here. What are the major Federal players in funding anti-aging research right now? You know, I'm aware that the National—well, the National Academies have been ongoing for a while. The National Science Foundation has a—an effort going on. And so what are the major players both nationally and internationally in this? Dr. Niedernhofer, do you want to take a swing at that?

Dr. NIEDERNHOFER. Sure. So definitely the National Institutes of Health, in particular, the National Institutes on Aging. I would also give credit to NCI (National Cancer Institute), the Cancer Institute. They are thinking deeply about the interface of cancer and aging, as well as other institutes within NIH. The National Academy of Medicine has been very forthcoming in tackling aging. They've just written an incredible geroscience white paper that's available publicly. We see a lot of philanthropies trying to get involved. And I should also point out that the Office of the Director at NIH is investing in a lot of related projects analogous to the Human Genome but more focused on aging. So for instance, the SenNet Consortium that's addressing senescent cells, trying to characterize them so we can ultimately develop better therapeutics targeting them. So I think there's a lot of opportunity. I think what's really important for legislators is to keep this democratized so this is not something that's just swept away by wealthy individuals but instead, we learn about the biology of aging across very diverse groups of individuals so that everybody can benefit from this research.

Chairman FOSTER. Yes. Are the majority of these candidate drugs involved as senolytics, are these small molecule off-patent drugs that are likely to be fairly cheap to provide, or are there—they're going to be very—any feeling on how expensive these would be?

Dr. NIEDERNHOFER. That is a great question. So right now, we have largely in the field, particularly in academics taking financial support from Federal funding for our research, we've really focused on natural products, as well as repurposing existing drugs. And they're—the main rationale for that is these are going to be faster to test in a clinical setting because they—we can jump right in with a phase 2 clinical trial and not have to start from ground zero where we're just proving safety. So this is speaking to the urgency that we recognize. They are relatively inexpensive because these are either drugs that are FDA-approved but not prescribed or off patent, or natural products that are relatively inexpensive.

So the one I can provide actual numbers on is we've been working with Fisetin. It's advanced at clinical trials. It's about $15 a dose, and you need two doses every two weeks, so quite inexpensive.

Chairman FOSTER. Yes, because one of the things that we wrestled with policy-wise is that they're—you know, for a drug which

is off patent, there's very little commercial incentive to go and pay for the clinical trials. I was just wondering if that's something where we're actually just going to need government money to make sure the promising drugs are carried through to clinical trials because the absence of a commercial incentive.

Dr. NIEDERNHOFER. I do think it would be the responsibility of the Federal Government to get this started. I think it's also really important to de-risk this approach. As Dr. Horvath was saying, you know, it's a challenge right now because of the regulatory system as well. We don't have a way to approve a drug to extend healthy aging. And so proof of principle and advancing some of these inexpensive therapeutics that everyone can access, it would be fabulous to have Federal support for that.

Chairman FOSTER. Thank you. And I guess I will just yield to the Ranking Member at this point.

Mr. OBERNOLTE. Thank you, Mr. Chairman.

Dr. Horvath, I wanted to ask about a part of your testimony you were discussing that there will be a need for a new regulatory framework for the treatment of healthy people, as opposed to our current regulatory framework that's geared more toward treating people who are ill. I wondered if you could—that's very much our bailiwick, and it's something that's going to be useful for us to start thinking about. Can you talk about what a framework like that would look like and how it would differ from the existing framework that we have?

Dr. HORVATH. I think it would be important to develop different metrics of measuring success. And the reason is, imagine you have a drug that you give to a middle-aged person, a 40-year-old, with the hope that it will prevent many future diseases. But then you, of course, would have to follow this person for decades. And it's cost prohibitive. So in order to advance medications that prevent the onset of these age-related diseases, we need to find surrogate metrics, as opposed to actual disease states, in other words, biomarkers. And it would be very good if a regulatory agency could take the lead, to organize a panel and really carefully look at the data, generate additional data, and develop surrogate markers, what we call surrogate endpoints that are trustworthy, that most scientists believe in. But then also these should be available then to the biotech industry so that it unleashes investment from private sources to fund these trials.

Mr. OBERNOLTE. Right. Actually, Dr. Niedernhofer, let me ask you about that as well because in your testimony you were talking about one of the barriers to the advancement of geroscience being the lack of aging biomarkers, and it seemed like if we had—I think that's exactly what Dr. Horvath is discussing, you know, that we would need these aging biomarkers to be able to prove the therapeutic benefit that would need to fit into the regulatory framework of healthcare. So could you talk about what those biomarkers might look like and how we can—how we can eliminate that barrier?

Dr. NIEDERNHOFER. Yes. And I have deep respect for the biomarkers—the epigenetic biomarkers that Dr. Horvath has developed. I think they are some of the key tools in our toolbox, but we need more. And I think it even stems from trying to assess what

people value in old age across very different ethnic and social economic groups, just understanding what they value, what their goals are, starting there, so there could be functional tests that we have, how quickly you walk, how quickly you get up and down out of a chair, what's the slow decay in your ability to do a lap around the track. It should also incorporate molecular markers that are very quantitative, and we have a lot to learn here. But I think it should start really with a conversation between regulators, what they need to prove safety, efficacy, and then the scientists who can actually figure out how to measure those and develop those tools.

So I agree with Dr. Horvath that it'd be lovely to have panel discussions where we really anticipate what's going to be needed to compress the length, the duration, and the size of these clinical trials so that we can afford them and do it in an iterative process, maybe even in parallel, so that we're able to test many different approaches and really come up with an answer to extend healthy healthspan as quickly as we can.

Mr. OBERNOLTE. Just playing devil's advocate, though, I mean, I think we're talking about something more than just measuring a deterioration that occurs with aging. And I mean, for example, I'm feeling very old this morning because I had congressional football practice, and my body's reminding me that—that it's not the same body that it was 30 years ago when I actually played football. But, I mean, you could measure my time running around a track, and it certainly has decayed in the last few years. But the whole purpose of a therapeutic treatment is so that that will not decay, right? So you wouldn't have that marker, right? So we need something cellular that provides, you know, a marker for the efficacy of the treatments that we're proposing to be able to—you know, to fit into the regulatory framework we have. I mean, don't we?

Dr. NIEDERNHOFER. We absolutely do, but I do believe as well that you need to tie it to some functional outcome so that you really—the individual is experiencing the benefit as well.

Dr. HORVATH. I could add a few comments. Aging really starts very early on. On a molecular level, children already age in some shape or form. And so it is correct, we do we need these early molecular biomarkers as well.

I want to add another point, which is when you put two scientists in the room, you will get two different opinions. They will never agree on which biomarkers should be used. So there's really a need for leadership, regulatory leadership, and impartial leaders making decisions, executive decisions, informed decisions, decisions based on data, rigorous testing, but leadership would help the field tremendously.

Mr. OBERNOLTE. All right. Well, thank you very much. I yield back, Mr. Chairman.

Chairman FOSTER. Thank you. And we'll turn it over to Representative Perlmutter.

Mr. PERLMUTTER. Dr. Olshansky, I've got a couple of questions for you. So this morning, I was going through my news feeds, and one of the articles that pops up is "90 will be the new 40 in 10 years," you know, which, again, is I'm, you know, at 69 sort of marching—time keeps marching on. That's—that was music to my ears in looking at that. But there are—one, is that—do you think

that's a legitimate headline? And to the other panelists, you can answer that, too. But my second question would be more, again, going back to the macroeconomics of this, you know, to Social Security and things like that. If in fact we are moving forward where people can live longer, healthier, more productive lives, then there are some things on a macroeconomic level that we need to prepare for, one of those being Social Security. So I'll just let you respond generally to both of those questions.

Dr. OLSHANSKY. Yes, so I'll respond to the second one first. So look, when geroprotectors come online, they will indeed successfully produce more healthy older people. There will be more people surviving past the age of 65, 85, 90 than any time in history, in part as a result of these therapeutics, so Social Security will be challenged. There's no question that the Social Security Administration is going have to deal with a larger population that will be drawing benefits for a longer time period.

However, if we're extending healthy life and people decide to work longer and it will be their option, you will now have justification for delaying age at entitlement, whether we're pushing back 62 and 67, by how much, there would certainly be logical justification for altering age at retirement, and that would certainly deal with the issue associated with more healthy, older individuals drawing from Social Security.

I saw the same story you saw, by the way, on "90 is the new 40 in 10 years." It's the 10 years, by the way, that bothers me. The 10-year claim has been made for 2,000 years, you know, that some magical breakthrough is going to happen in exactly 10 years. So the 90/40 might be a bit of an exaggeration, but the concept, I think, is right on target. And that is, it will take a longer time period to grow old biologically. Maybe, you know, it'll take 90 years to become 70 or 80 years to become 60 or something along those lines, but practically, at our level, the way in which you and I and all the listeners operate, we will experience biological time at a slower rate. A year from now you will not be a year older. You might be nine months old, or eight months older. It's not going to stop aging; it's going to slow it down. And in the end, that's what we want is to retain our youthful vigor for a longer time period.

So some of the numbers—I don't like this embellishment and exaggeration that I see in the field all the time. But the overall premise, I think, may be on target.

Mr. PERLMUTTER. Well, I'm smiling because we have this thing at the YMCA called the e-gym, where it sort of tracks you and all this stuff, and it has biological age. This makes me very happy when I look at it. It says my legs are 36 years old, my core is 35, and my chest and arms are 27. So to any future employers, I give them this, say, look, there's a lot of years left in this guy.

So, you know—but I think what you're all talking about is that there are potential scientific breakthroughs, whether it's through the use of biomarkers to kind of manage things or metformin or whatever the drug was that was mentioned. But there are also other things that we're becoming, you know, smarter about in terms of nutrition and exercise and those kinds of things, which, again, Dr. Niedernhofer, you know, we're trying to both have quantitative objective kinds of markers but also there's a qualitative ele-

ment to this is, you know, does it hurt every time you get up out of a chair? So I don't know if you have any comments either to my biological age, which I think is pretty good, or otherwise?

Dr. NIEDERNHOFER. Well, I would say congratulations. And we need to continue to build these tools so that we can do this for everyone and accurately. I don't completely trust the tools that we have entirely at this point, but obviously——

Mr. PERLMUTTER. Well, I do.

Dr. NIEDERNHOFER [continuing]. You're good. You're on a great trajectory.

The other thing I would just comment about sort of in terms of the economy is just picture a person who's in memory care versus a person who's independent, which I think is what geroscience approaches can achieve, a little, you know—an extended period of independence and activity. So they are going to contribute one way or another to the economy much more so than somebody who's sadly trapped in memory care.

Mr. PERLMUTTER. Thank you. I yield back to the Chair.

Chairman FOSTER. Thank you. And it's—I believe we can actually have another quick round of questions because this remains fascinating. So—and I will now recognize myself for five minutes.

What is the current understanding about the evolutionary advantages for senescence? Because that has me really confused. You know, apparently, some species like lobsters do not have senescence and then others do. What is believed to be the advantage of why this is as evolved?

Dr. NIEDERNHOFER. I believe this is a question for me?

Chairman FOSTER. Go for it.

Dr. NIEDERNHOFER. Thank you. So senescence evolved as a tumor-suppressor mechanism. In my mind, it is one of the most potent anticancer programs we have in our body, so it's necessary for multicellular organisms that live a very long time. So if a cell is stressed, in particular, the DNA of that cell is stressed, if that cell will respond by activating signals that say I will never copy myself again and make a new cell, and that prevents that damaged stress cell from turning into a tumor. So it's very advantageous.

We also know that there's senescent cells in a number of physiologic, healthy contexts. So during wound healing, obviously, there's a stress to your skin if you're cut open, and senescent cells will accumulate at that site to help heal it. But these are very acute events that are cleaned up and help you carry on without having the chronic inflammation that can come with building up senescent cells with aging.

We think part of the problem with senescence in old age is that senescent cells just accumulate because your immune system, the function of it declines a bit with aging, and therefore, you're unable to receive signals from the senescent cells that call in your immune system to clear them. So it's a lovely cancer-protection mechanism, contributes a lot to various physiologic states in mammals, but turns against us as we get older, as many things do in biology of aging.

Chairman FOSTER. So do you see the mechanism throttled down in, you know, elephants versus mice? Or is it a pretty universal pattern there?

Dr. NIEDERNHOFER. So that's a great question. So we've learned a lot from comparing different species. And indeed, elephants are some of the longer-lived species. They have extra copies of genes that reduce their cancer risk, and therefore, they just experience much less cellular senescence. But there's still a lot to learn in this space. And I think we're a little bit caught up in just lack of definition of a true senescent cell. It's very hard in my mind to talk about healthy senescent cells and pathologic senescent cells and not get everybody confused.

Chairman FOSTER. Yes. Was there someone else who wanted to comment?

Dr. OLSHANSKY. Yes. Yes, if that's OK. So really good questions, by the way. So this issue of humans and elephants and dogs and how long we live and why it's all relevant is actually central to the study of aging and longevity. But keep in mind, we cannot have aging or death programs that evolved within us. We don't have a ticking time bomb that goes off at a certain time period. Natural selection could not have led to the evolution of ticking time bombs in our body. So think of aging and senescence as an inadvertent byproduct of fixed genetic programs that exist for growth, development, and reproduction. And that explains why different species live different lifespans. You know, dogs live, you know, about 15 years, and they go through puberty at nine months. They go—you know, their reproductive window is much shorter. Our reproductive window is longer. We live longer as a result. So there's this calibration between duration of life and the reproductive window of the species.

But importantly, there isn't a death program. And the absence of a death program is the reason why we can intervene. It's the reason why these geroscience interventions are going to work, and it's also the reason why diet and exercise can actually have an influence on how healthy we are and how long we live as well. The field is wide open for intervention.

Chairman FOSTER. Now, are there examples of where the extension of the healthspan is not associated with the extension of lifespan in any animal studies or so on? Are these—you know, it's a very—you know, politically, it solves a lot of problems if the main result of these—all these treatments is that you're healthy longer, and then you die at pretty much the same time? If it is—if that's not really the case, then it's a much more complicated set of policy implications. So what's the best understanding of that relationship?

Dr. OLSHANSKY. I can comment real quickly. I think that when we introduce these geroprotectors, we know that we will see a compression of morbidity and disability. By how much exactly, I think we cannot yet determine. We will need the biomarkers to make that determination. The unanswered question, which I think is the one that you're addressing, is how much longer might we live as a result? And we don't know yet how much longer we will live as a result. And keep in mind, when scientists and others come along and suggest we're going to live 10, 20, 30, 40, 50 years longer as a result, there's no evidence to support that at all. We cannot—that is an untestable hypothesis on any sort of radical life extension proposal that folks are making. So that's one of the reasons why

we're focusing in on healthspan. It's something we can measure and we can detect very quickly in these types of studies.

Chairman FOSTER. So I guess I was asking about animals. Any any hints from smaller animals? Dr. Horvath?

Dr. HORVATH. Yes, you know, I've looked very carefully at epigenetic determinants of what I call maximum lifespan in species. We have analyzed 348 mammalian species, from the maximum lifespan two years in a shrew to the bowhead whale, whose maximum lifespan is 211. And there is a strong epigenetic signal. But the interesting finding was that whatever determines maximum lifespan was actually quite different from what relates to human mortality risk. So my opinion is that the determinants of maximum lifespan are quite different from what we care about here, which is healthspan.

Chairman FOSTER. All right. Thank you. And I'll yield to the Ranking Member.

Mr. OBERNOLTE. Thank you, Mr. Chairman.

Dr. Niedernhofer, we were talking a few minutes ago about the barriers to the advancement of geroscience that you had brought up in your testimony. And one of the barriers that you mentioned is lack of public knowledge. Can you talk a little bit about why that's a barrier and what we can be doing about that?

Dr. NIEDERNHOFER. Yes, thank you for asking. I just feel that it's a little bit of a rarefied crowd that really understands geroscience at this point. And I feel like we need to gather a lot more information from various stakeholders in the United States to understand what they value in old age and how we can address their needs as well. This may not be for everyone. I think deeply about Native Americans who can't wait to get old and be an elder in their community, and they don't want to interfere with that process. So I think we need to gather information and educate people to get buy-in because I think there's an awful lot of these people who would be tremendously excited about it, but we need to understand across our population who—you know, what the various opinions are about this approach.

Mr. OBERNOLTE. Well, I mean, I think, also, maybe caution is warranted because, as Dr. Olshansky just pointed out, we don't have any scientific evidence that we can extend lifespan. We just know that we have these cellular epigenetic clocks that, you know, we think we can—we think we can eliminate. And we also think that maybe we can reverse some of the effects of aging such as Alzheimer's disease, which, you know, would have—by itself would have a huge—a huge benefit for society. But, you know, we really can't promise people anything. And I actually think that if we're—when people hear about this, they could be tremendously excited. It's just that, you know, we have to be very cautious about being realistic with them about what we can and can't promise.

So, anyway, I thought that was interesting. But that would—I mean, to your point, that would help eliminate some of the other barriers that you brought up, you know, certainly, lack of scientists, if we evangelized, you know, this emerging field better, we could get more young people in training and fields to be able to do this kind of research. Lack of funding, certainly, you know, a greater public awareness would help us with that.

Dr. Horvath, we—the Chairman was having what I thought was a really interesting discussion about—about clinical trials and how they're funded, given that many of the drugs that we are investigating in—for the use of geroscience are off patent, and that eliminates a profit incentive for private industry to fund those. So, you know, we're funding research through NIH, we're funding research through NSF. Do you think that this is a barrier to actually bringing therapeutics to market? And if it is, then how much more funding do you think we would have to do?

Dr. HORVATH. Yes, just to echo what you said, it would be wonderful if we found incentives to repurpose existing drugs or drugs that are off patent, natural products. Now, I'm thinking about how to do it, you know. I really don't have a good solution, unfortunately. But yes. So many scientists really work on that. I want to say most scientists in the geroscience field actually work on that. Why? Because natural products are safe. And also to remind everyone, when you go back to a dinner party and talk about aging, everybody will share their favorite supplements with you. What are they taking? Vitamin D, whatever. And what is so frustrating to me personally is everybody has their favorite one, but the evidence is so weak. And it would be wonderful then if we found ways to do rigorous studies of these supplements that so many of us are taking. And yes, I'm not sure whether I answered your question.

Mr. OBERNOLTE. Well, you know, it's—it might be a problem that solves itself because once the—we can state credibly that there are health benefits to doing this, there's going to be incredible public interest and public demand for this. And so that's going to create a market void for companies to fill. And, you know, that'll be a source of private funding, so we'll see.

Well, it's been a fascinating discussion. In closing, though, I want to comment on Congressman Perlmutter's biological age and just point out how much we've enjoyed having him here on the Committee. And since the biological age is so low, you definitely should not be, sir, retiring from Congress. I yield back, Mr. Chairman.

Chairman FOSTER. Yes, we'll be using the Yamanaka factors to clone Perlmutter. So it's all underway. OK. Representative Perlmutter.

Mr. PERLMUTTER. All right. I thank the gentleman.

You have used, all of you, a euphemism of compression of morbidity, which I'm not—as a lawyer, I'm going, OK, what the heck does that mean? Does that mean when you die it happens quick or—I mean, Dr. Olshansky, I think you've used it the most. So tell me what it is you mean by compression of morbidity and why that's an important concept.

Dr. OLSHANSKY. Yes, great question. So it basically means everything that goes wrong with our bodies and our mind with the passage of time would be delayed. If normally you would see an expression of a particular disease or a disorder at age 60 or 70 or 80, it might be delayed to 70, 80, or 90. And when things go wrong, they would happen more rapidly.

And so it's—actually, it's a fairly straightforward concept, and it's not foreign to us because we already see it among subgroups of the population that exist today. It's about 15 percent of the U.S. population called super agers. And these are individuals that make

it out past the age of 80 cognitively intact. You can't really tell the difference between them and a 40- or 50-year-old. And so we see it today among subgroups of the population that are already experiencing morbidity and disability compression. They're healthy, they're active, they're exercising, they can be president, they can be CEO (Chief Executive Officer), they can do whatever they want. And it's 60, 70, 80, 90. And it's already here today among subgroups.

So it's what we want. It's a healthier life for a longer time period. And basically, age becomes just a number. It becomes largely irrelevant. And when things go wrong, they go wrong quickly. And so it's not going to stop us from aging. It's not going to stop us from dying at some point. But it will lead to a longer period of youthful vigor. And in the end, certainly, that's what my father told me when he was in his 90's. He said all he wants is his health. And I couldn't agree with him more. It is the most precious commodity, and that's what this is all about is extending the amount of this precious commodity that all of us have in life.

Mr. PERLMUTTER. Well, I want to thank you. I want to thank your fellow panelists. This has been fascinating. I think that's a good place to close. I'll yield back to the Chair.

Chairman FOSTER. Thank you. And now, before we bring this hearing to a close, I want to just thank our witnesses again for testifying before the Committee. The record will remain open for two weeks for additional statements from the Members and for any additional questions the Committee may ask of the witnesses.

And the witnesses are now excused, and the hearing is now adjourned.

[Whereupon, at 11:18 a.m., the Subcommittee was adjourned.]

Appendix I

Answers to Post-Hearing Questions

ANSWERS TO POST-HEARING QUESTIONS

Responses by Dr. Jay Olshansky

If an effective anti-aging therapy were to become widely available, the implications for the labor force, for retirement, for pension funds, for insurers, and for the healthcare and eldercare communities would be significant.

a. When is the right time to begin a dedicated interdisciplinary conversation that engages economists, actuaries, and ethicists with molecular biologists and physicians about these projected impacts?

The time is now. Dr. Sierra and Dr. Kohanski set the wheels in motion for this discussion through the National Institute on Aging, but the main sources of funding for Geroscience are focused entirely on the development and testing of a therapeutic intervention. I would strongly encourage those involved in supporting this effort to think ahead to the social, economic, and health consequences of success and failure.

b. What forum is most appropriate to coordinate a formal interdisciplinary dialogue? Do you feel that ongoing efforts at the National Academies of Science, Engineering, and Medicine are sufficient? Should the Office of Science and Technology Policy be engaging at this time?

The former head of the Office of Science and Technology Policy under President Obama – Tom Kalil – is acutely aware of the Geroscience initiative. He would be the perfect person to contact regarding discussions of which organizations should be involved in coordinating this interdisciplinary dialogue.

You mentioned in your testimony that one application of aging therapies would be to protect astronauts from high risks associated with exposure to radiation.

a. Should ongoing NASA research on radiation exposures be expanded to include Geroscience research?

According to Dr. Kirkland from the Mayo Clinic, work is already underway with Axiom Space and SpaceX to explore the potential benefits of senolytic compounds and other aging interventions that could lower health risks associated with astronaut exposure to even low levels of radiation. I don't know if NASA is directly involved with any of this ongoing or planned research through the TGN, but it would make sense that these connections be made expeditiously – especially if plans are underway for astronauts and space tourists/ employees to spend extended time in space for any reason.

b. Would the health data of civilians who chose to travel to space and are exposed to space radiation be helpful to Geroscientists seeking to understand regular aging on earth?

Studies of possible accelerated aging among civilians or others that spend any significant amount of time exposed to radiation should be relevant to understanding aging on earth. The same applies to people in occupations that exposure them to elevated amount of radiation, such as airline pilots and flight attendants.

Alternatively, it would make sense to utilize Geroprotectors to improve health and safety among anyone involved in space tourism. For example, if space tourism in the future leads to days or weeks spent outside of Earth's atmosphere, it would be wise to have some level of protection – just as dentists do with their patients that are protected from low dose radiation using lead shields when x-rays are taken. Given that radiation exposure represents a cumulative health risk, it might also make sense to determine whether airline pilots, flight attendants, and employees working with radiation in the health industry, have elevated occupational exposures to radiation; and if so, these might be an appropriate endpoint for Geroprotectors.

It may also be relevant to consider Geroprotectors for patients when radiation is used to treat various forms of cancer.

Thus, it would be helpful to learn about human aging in general from civilians involved in space travel/tourism; and it would make sense to utilize Geroprotectors to protect everyone exposed to radiation for any reason.

I understand the geroscience community would like to eradicate the words "anti-aging." 1. Please expand on this. Does the legacy of anti-aging gimmicks make your job as a legitimate scientific researcher more difficult?

The term "anti-aging" has been used by an industry that has arisen that is trying to sell products to the public before being tested for safety and efficacy – it's called "anti-aging medicine". Their presence makes the lives of scientists in the field far more difficult because they take research papers from established scientists, embellish the results and present them to the public as fact, and then begin manufacturing and selling "anti-aging products" to the public under the banner of medicine or science. This is equivalent to someone selling an alleged Covid-19 vaccine to the public shortly after mRNA technology is discovered; but before the clinical trials are begun or completed to test for their safety and efficacy – with no safeguards in place to ensure the vaccines are manufactured using safety standards. It's a serious problem in our field.

The U.S. Senate was acutely aware of this issue. They held Senate hearing 107-190 (Swindlers, Hucksters and Snake Oil Salesman: Hype and Hope Marketing Anti-Aging Products to Seniors) on September 10, 2001, but this report was lost in the news cycle as it appeared at the same time as 9/11.

b. How can the policy community help separate the serious science from dubious marketing claims?

Regarding what's required by the policy community, this should begin by recognizing that there are no Geroprotectors ready for prime time yet, so anyone selling anything resembling an aging intervention today means they're doing so before the intervention has been tested for safety and efficacy. People in this shadow industry are making money by encouraging people to experiment on their own bodies using unproven and often untested interventions; and there are no safeguards in place to ensure that the products being sold through the anti-aging "medicine" industry actually contain any of the alleged active ingredients and no ingredients that may be harmful to health.

When safe and effective legitimate Geroprotectors enter the health marketplace, they will be accompanied by approvals from the FDA for targeted health endpoints, and details on manufacturing standards and the results of clinical trials that tested the interventions for safety and efficacy.

Responses by Dr. Laura Niedernhofer

EDDIE BERNICE JOHNSON, Texas
CHAIRWOMAN

FRANK D. LUCAS, Oklahoma
RANKING MEMBER

Congress of the United States
House of Representatives
COMMITTEE ON SCIENCE, SPACE, AND TECHNOLOGY
2321 RAYBURN HOUSE OFFICE BUILDING
WASHINGTON, DC 20515–6301
(202) 225–6375
www.science.house.gov

September 30, 2022

Dr. Laura J. Niedernhofer
Professor
University of Minnesota
6-155 Jackson Hall
321 Church St. SE
Minneapolis, MN 55455

Dear Dr. Niedernhofer:

On behalf of the Committee on Science, Space, and Technology I want to express my sincere appreciation for your participation in the September 15, 2022, hearing entitled "*The Fountain of Youth? The Quest for Aging Therapies.*"

We have attached a transcript of the hearing for your review. The Committee's rule pertaining to the printing of transcripts is as follows:

> *The transcripts of those hearings conducted by the Committee, when it is decided they will be printed, shall be published in substantially verbatim form, with the material requested for the record inserted at that place requested, or at the end of the record, as appropriate. Individuals, including Members, whose comments are to be published as part of a Committee document shall be given the opportunity to verify the accuracy of the transcription in advance of publication. Any requests by those Members, staff, or witnesses to correct any errors other than errors in the transcript, or disputed errors in transcription, shall be appended to the record, and the appropriate place where the change is requested will be footnoted. Prior to approval by the Chair of hearings conducted jointly with another Congressional Committee, a memorandum of understanding shall be prepared which incorporates an agreement for the publication of the transcript.*

Transcript edits, if any, should be submitted by **Thursday, October 13, 2022**. If no edits are received by the above date, we will presume that you have no suggested edits to the transcript.

All transcript edits and responses to questions should be submitted to us and directed to the attention of Hannah Robinson. If you have any further questions or concerns, please contact Hannah Robinson at Hannah.Robinson@mail.house.gov or at (202) 225-6375.

Please also take the time to complete a voluntary survey to help Congress better understand the backgrounds of the witnesses who appear at Congressional hearings. Your participation in this survey helps Congress ensure that our policies and legislation are inclusive and work for Americans of all backgrounds. All data remains anonymous and protected according to the United States House of Representatives' policy and data security practices. The survey can be found at the following link: Witness Diversity Survey.

Sincerely,

Bill Foster

Chairman Bill Foster
Subcommittee on Investigations and Oversight
Committee on Science, Space, and Technology

Enclosure: Transcript
Attachments: Questions for the Record

U.S. HOUSE OF REPRESENTATIVES
COMMITTEE ON SCIENCE, SPACE, AND TECHNOLOGY
SUBCOMMITTEE ON INVESTIGATIONS & OVERSIGHT

Questions for the Record to:
Dr. Laura J. Niedernhofer
Professor
University of Minnesota
Submitted by Chair Bill Foster

1. If effective anti-aging therapy were to become widely available, the implications for the labor force, for retirement, for pension funds, for insurers, and for the healthcare and eldercare communities would be significant.

    a. When is the right time to begin a dedicated interdisciplinary conversation that engages economists, actuaries, and ethicists with molecular biologists and physicians about these projected impacts?

In my opinion, starting these conversations cannot come soon enough. It will require, as stated, very diverse disciplines and voices to envision the potential impact of geroscience approaches to treating the elderly. These conversations will be challenging as all stakeholders will enter the conversation with biases based on their training and life experiences. The required disciplines use different languages that make it challenging to communicate and to critically analyze one another's approaches and conclusions. Hence, in my view, this is a task of the size and complexity that requires federal support. Ideally, these conversations would run in parallel with continued progress in translating geroscience approaches so that we can continue to collect data to inform predictions and policy.

Based on models that are, admittedly, still sparse, my hunch is that the results of said conversations will overwhelmingly support pursuing geroscience approaches because of the quality of life (personal and societal) and financial gains. Here are a few examples of those models:

The *majority* of individuals over 65 have multiple co-morbidities. As the elderly population continues to expand, under the current paradigm of treating one disease at a time, *health care costs will increase dramatically* but with negligible impact on the overall health of our population. Ihttps://pubmed.ncbi.nlm.nih.gov/30242384/

Medicare spending (as a share of GDP) is predicted to double by 2050 due to our aging population. If geroscience approaches are applied and successfully delay aging, it is estimated that the additional cost in entitlement programs will be ~$300B in 2060 due to more elderly people being alive. However, the societal benefit is estimated to be >$7T. https://pubmed.ncbi.nlm.nih.gov/24101058/

Currently, >70% of deaths in the USA are caused by chronic, non-communicable diseases. It is impossible to change this number significantly by trying to cure one disease at a time. In contrast, geroscience approaches, which target these diseases *collectively*, are estimated to have a return of $38T for each additional year of health gained. https://www.nature.com/articles/s43587-021-00080-0

In 2019, the global economic burden of Alzheimer's disease and related dementias (ADRDs) was an estimated $2.8 trillion. This projected to increase to $16.9T in 2050. At which point, low- and middle-income countries will account for 65% of the global economic burden, compared to 18% in 2019. Upper-middle income countries will shoulder the largest economic burden of this shift (60% of global burden). https://pubmed.ncbi.nlm.nih.gov/35898316/

U.S. HOUSE OF REPRESENTATIVES
COMMITTEE ON SCIENCE, SPACE, AND TECHNOLOGY
SUBCOMMITTEE ON INVESTIGATIONS & OVERSIGHT

Questions for the Record to:
Dr. Laura J. Niedernhofer
Professor
University of Minnesota

Similarly, I do not believe we have good understanding of what will happen to the labor force, pension funds, insurance, healthcare, and eldercare if we maintain the status quo. This too could be analyzed through dedicated conversations by the same stakeholders. I predict the outcome of those discussions would be alarming enough to garner substantial support from constituents for pursuing geroscience.

b. What forum is most appropriate to coordinate a formal interdisciplinary dialogue? Do you feel that ongoing efforts at the National Academies of Science, Engineering, and Medicine are sufficient? Should the Office of Science and Technology Policy be engaging at this time?

In my opinion, the Office of Science and Technology Policy should be engaged in this dialogue and would be the best leader for consolidating information gathered government-wide to inform domestic priorities and policies. Aging biology affects *every person* and *every aspect* of life. Hence, it would be extremely valuable to gather information from experts in communication, housing and urban development, transportation, health and human services, education, veteran's affairs, and the FDA, as well as NSF and *all* NIH Institutes and Centers.
The National Academy of Medicine recently created a Global Roadmap for Healthy Longevity. https://nam.edu/initiatives/grand-challenge-healthy-longevity/global-roadmap-for-healthy-longevity/. The key recommendation of the report is to initiate dialogues between governments and diverse stakeholders in order to *create new policies* to address the needs of our aging population, including topics such as work environments, social infrastructure, education, mitigating ageism, financial security, and equitable/culturally sensitive care. This will require buy-in across the entire federal government.

2. You said in your testimony that a lack of biomarkers is a primary impediment to progress in geroscience therapies. How can the federal research enterprise best contribute to the development and evaluation of reliable biomarkers?

We do need surrogate biomarkers for lifespan and healthspan that are rigorously tested, easily quantified, and tied-to clinical endpoints that are meaningful to people. These will be imperative for making geroscience-driven clinical trials efficient and economical. In my opinion, fostering dialog between multidisciplinary experts would be invaluable to accelerate and prioritize biomarker development and implementation. The discussion should include experts in aging biology, clinical practitioners, clinical trialists, sociologists, statisticians, engineers, and the FDA who collectively can address feasibility, practicality, acceptability across cultures, and economy.

U.S. HOUSE OF REPRESENTATIVES
COMMITTEE ON SCIENCE, SPACE, AND TECHNOLOGY
SUBCOMMITTEE ON INVESTIGATIONS & OVERSIGHT

Questions for the Record to:
Dr. Laura J. Niedernhofer
Professor
University of Minnesota
Submitted by Representative Ed Perlmutter

1. I understand the geroscience community would like to eradicate the words "anti-aging."

    1. Please expand on this. Does the legacy of anti-aging gimmicks make your job as a legitimate scientific researcher more difficult?

Correct - anti-aging conjures images of being *against* aging and carries a very negative connotation that promotes ageism. Aging is inevitable, at least in this part of human history. Thus, we do not want to make aging a negative part of the human experience. As geroscientists, we aim to slow aging rather than eradicate, prevent, reverse, or undo aging. There are plenty of "snake-oil salespeople" who make aging science challenging. But that is inevitable when there are high stakes and potential financial gain.

    2. How can the policy community help separate the serious science from dubious marketing claims?

I believe a solution to the anti-aging culture is to create a clear definition of geroscience, the biology behind it, its purpose and potential. If the policy community could help create that concise message with input from diverse experts and disseminate that message broadly, it would be very valuable for engaging professionals who are not used to considering the impact of our aging society on their industry, while garnering the support of healthcare providers and those they care for.

Responses by Dr. Steve Horvath

To: House of Representatives
Committee on Science, Space, and Technology
To Chair: Dr Bill Foster
Attention: Hannah Robinson.

From: Dr. Steve Horvath
(shorvath@altoslabs.com)
Principal Investigator
Altos Labs Inc, San Diego

RE: Response to Questions For the Record
October 13, 2022

Dear Chair Dr Foster, Representative Perlmutter, and Members of the Committee,

Thank you again for giving me the wonderful opportunity to participate at the hearing on "The Fountain of Youth? The Quest for Aging Therapies." (September 15, 2022).

Please find below my responses to the questions of the committee members (colored in blue).

Best wishes for staying young and healthy,

Dr. Steve Horvath
Principal Investigator
Altos Labs

Response to Questions submitted by Chair Bill Foster

1. If effective anti-aging therapy were to become widely available, the implications for the labor force, for retirement, for pension funds, for insurers, and for the healthcare and eldercare communities would be significant.

a. When is the right time to begin a dedicated interdisciplinary conversation that engages economists, actuaries, and ethicists with molecular biologists and physicians about these projected impacts?

Response by Steve Horvath:
I am not a policy expert, but when I consider this question, it is important to remember that we already have many therapeutics that extend lives – such as those that control blood pressure or lower glucose levels. As with the therapeutics already available, a timely interdisciplinary approach is important as well as an approach that allows the data to show where true impact on aging and healthspan can be made for individual therapeutics.

b. What forum is most appropriate to coordinate a formal interdisciplinary dialogue? Do you feel that ongoing efforts at the National Academies of Science, Engineering, and Medicine are sufficient? Should the Office of Science and Technology Policy be engaging at this time?

Response by Steve Horvath:
I am not a policy expert and don't feel qualified to suggest which is the right forum.

2. Aging clocks have the potential to become a fundamental tool for the broader research enterprise on aging interventions. They offer the prospect for clinical experiments to get results within months, rather than decades. Are there any other fundamental tools or strategies in need of further investment and development that would be similarly impactful on bottlenecks in geroscience?

Response by Steve Horvath:
I think we have a wonderful biomedical tool box available. CRISPR technologies, high throughput screening to find drug targets, powerful sequencing technologies that fuel the genomic revolution. Advances in artificial intelligence and computational methods.
We even have very promising interventions that slow the aging process in animal models.
The main bottleneck are the high costs associated with conducting human studies and clinical trials.

3. You said we can predict human age now using a simple blood draw.

a. Under what circumstances does someone's epigenetic clock suggest they are older than their chronological years?
Response by Steve Horvath:
Our best epigenetic predictors of mortality risk indicate that smoking, obesity, select infections such as HIV or COVID are associated with older age. Epigenetic clocks are associated with kidney disease, lung disease, fatty liver, even brain related changes.
Certain somatic mutations that predispose people to blood cancers have also been linked to epigenetic clocks.

b. Do you envision a future where your primary care physician would test your blood for aging biomarkers as routinely as they test your glucose or your blood pressure?

Response by Steve Horvath:
Yes, I envision such a future but we are not there yet. Additional rigorous studies will be needed to get us to this point. I'd hope if they are helpful in addressing the frailties and diseases associated with aging that they would be available for primary care physicians.

Response to Questions Submitted by Representative Ed Perlmutter

1. I understand the geroscience community would like to eradicate the words "anti-aging."
   1. Please expand on this.

   Response by Steve Horvath:
   Yes many people have an aversion to this word but I still use this expression since it is intuitive.
   The word "anti-aging" has certain connotations e.g. it is widely used in the cosmetics industry. The word anti-aging is often use to sell products and supplements for which the scientific evidence is lacking.
   What we call things can be important, but the most important thing is that we generate data, learn from it, and be willing to adjust the labels and notions we bring to our work if

that is what the evidence suggests we should do. To the extent that the jury is still out, debate is a good thing.

2. Does the legacy of anti-aging gimmicks make your job as a legitimate scientific researcher more difficult?

   Response by Steve Horvath:
   It is true that there are lots of claims and mythologies about aging. Wrong claims hurt the scientific enterprise. Not anymore. There has been a sea change because superb scientists have entered the geroscience field. Impactful peer reviewed scientific publications have greatly expanded our mechanistic understanding of the aging process. I am confident that we can separate the true breakthroughs from the noise through quality experimentation and data.

3. How can the policy community help separate the serious science from dubious marketing claims?
   Response by Steve Horvath:
   I am not a policy expert nor can I speak to commercial marketing practices. But generally speaking, the policy community should look at the data generated in robust and well-controlled clinical trials to provide you with a path to the serious science.

   Thank you again for your interest.

   Best wishes,
   Steve Horvath

Appendix II

Additional Material for the Record

Letter submitted by Representative Bill Foster

Statement from the Buck Institute for Research on Aging, Novato, CA

For Inclusion into the Proceedings of the Subcommittee on Investigations and Oversight of the House Science Committee, September 15, 2022

"The Fountain of Youth? The Quest for Aging Therapies"

The Buck Institute for Research on Aging applauds the House Science Committee for holding this critically important hearing. As the world's first and leading independent research organization focused solely on research on aging, the Buck understands how advances in this field will have a game changing impact on the practice of medicine as well as on a multitude of social and economic policies. We are delighted that the Committee is focusing on geroscience, the intersection of the biology of aging and age-related diseases. This is in fact a term that originated at the Buck in 2007.

Aging is the number one risk factor for a host of serious chronic diseases including Alzheimer's, Parkinson's, cancer, macular degeneration, heart disease, stroke, osteoporosis, osteoarthritis, and type 2 diabetes, all of which have an outsized impact on both human suffering and our healthcare system. We know that these diseases do not have to be an inevitable part of aging and that indeed, people can enjoy life, with healthy minds and healthy bodies, at 95 much as they do at 45. At the Buck, we are working every day to end the threat of age-related diseases for this and future generations by bringing together the most capable and passionate scientists from a broad range of disciplines to identify and find ways to impede the ways in which we age.

Buck scientists have made a host of breakthrough discoveries that are now being translated from the bench to the bedside. The future is bright but cannot be accomplished without federal support. Thank you to the Committee for your interest. We are committed to support your efforts to help us all live better longer.