

THE ALLIANCE FOR LONGEVITY INITIATIVES

A Policymaker's Guide to the Longevity Therapeutics Industry

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Executive Summary

The commercialization of therapies targeting aging will transform society in unprecedented ways. These revolutionary "longevity" therapies have the potential to prevent the diseases and disabilities of old age. They will dramatically increase society's healthspan, the length of time a person lives with vigorous, quality health. The U.S. will also reap the benefits of the so-called *Longevity Dividend*: our nation will create over \$38 trillion of value - through reduced Medicare and Medicaid spending, increased productivity, and GDP growth - by increasing Americans' healthspan by just one year. However, before the immense promise of these therapies can be realized, policymakers must pave the way for the coming revolution in healthcare.

This guide provides an introduction to the longevity and geroscience space for policymakers. The first section provides a brief overview of the "geroscience approach." It examines the nine hallmarks of aging and the effects of manipulating the hallmarks. By manipulating the hallmarks, therapeutics can be developed to treat the multitude of diseases related to aging all at once. This guide will also examine the longevity sector's history, current state, and promising therapies.

The guide's second section examines the various factors which should motivate the government's support of longevity medicine. There is the moral imperative: by supporting these therapies, the government will help to radically improve Americans' health outcomes. Additionally, there is the economic motivation offered by the Longevity Dividend Calculation. The section also touches on the geopolitical considerations for longevity therapies by examining the competitive advantage the U.S. stands to secure by establishing leadership in the field.

The third and final section proposes concrete actions Congress can take to support the development of longevity therapies. A4LI calls on Congress to:

- 1. Increase allocations to the National Institute of Aging Division of Aging Biology;
- 2. Make geroscience and longevity medicine a focus of ARPA-H;
- 3. Create a dedicated regulatory pathway for longevity medicines;
- 4. Fund Congressional Budget Office research into the longevity dividend; and
- 5. Initiate a national movement to increase healthy lifespan by setting an actionable, time-bound goal.

Society is on the edge of a revolution in medicine, but science alone cannot bring the country across the finish line. A4LI looks forward to working with policymakers to advance this cutting-edge field, a field that will improve the lives and future of the American people.



Longevity Therapies: A Scientific Explanation for Policymakers

Summary

While Americans' lifespan increased throughout the 20th Century, the rate of increase gradually slowed. In recent years, it has even reversed. Moreover, the majority of adults spend their final years battling at least one – and in many cases, several – chronic illnesses, greatly decreasing their quality of life.

Recently researchers have uncovered nine biological "hallmarks" of aging. When these hallmarks are aggravated, aging is accelerated. When they are mitigated, the aging process is slowed and the risk of developing diseases including cancer, diabetes, and Alzheimer's decreases. In this section, the guide will provide a brief overview of aging biology, and examine the growing number of companies seeking to harness existing pharmaceuticals, as well as next-generation technologies, to increase healthspan.

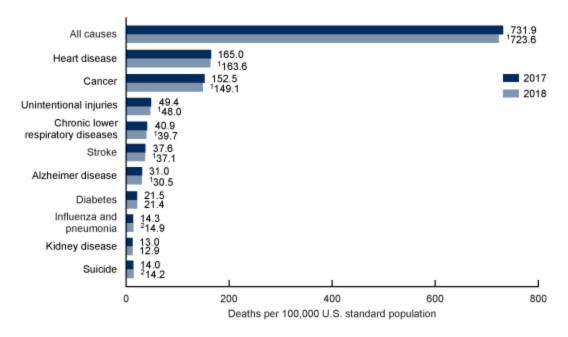
Longevity & the Geroscience Approach

Since the 19th Century, scientific and medical advances have driven a dramatic increase in life expectancy in the United States. However, since the start of the COVID-19 pandemic, life expectancy has dropped by more than two years, the largest drop since World War 2. Life expectancy fell by about 1.9 years in 2020, and – despite seeing rebounds in other developed countries – continued to drop by an additional 0.4 years in 2021. Life expectancy in the United States is now 76.6 years, more than five years less than the average among peer nations.¹ Additionally, despite increases in life expectancy, quality of life typically decreases rapidly as one gets older. Approximately 85% of adults over the age of 65 have at least one chronic condition, such as cancer, diabetes, heart disease, stroke, or Alzheimer's disease. 60% have at least two chronic conditions.² In many cases, the standard of care limits medical professionals to managing the symptoms of these diseases. In many cases, palliative care may be the only option. However, a new field of scientific research suggests that scientists may be able to effectively treat or even prevent serious diseases simultaneously by addressing the underlying cause: aging.



¹ <u>"US life expectancy continues historic decline with another drop in 2021, study finds."</u> CNN.

² "Supporting Older Patients with Chronic Conditions." National Institute on Aging.



Aging is a leading risk factor in diseases such as cancer, diabetes, heart disease, stroke, Alzeheimer's disease, and others. In fact, 70% of the nearly 8,000 deaths per day in the United States are caused by age-related diseases.³ Now, researchers have the potential to create a new class of medicinal therapies that reduce the likelihood of many age-related diseases by targeting the biological process of aging itself. By treating these diseases collectively, longevity therapies will not only increase the lifespan in the United States. They will also positively impact Americans' healthspan.

What is aging?

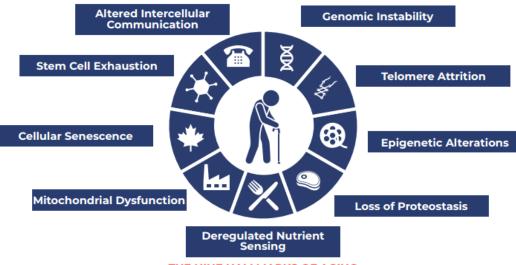
Aging is characterized by the gradual loss of physiological integrity, leading to impaired function and increased vulnerability to death from multiple causes. Geroscientists (scientists that study aging biology) have identified nine hallmarks of aging that are present in all organisms that age. Inducing these hallmarks accelerates the aging process, while mitigating them has been found to slow the normal aging process and, hence, increase healthspan.⁴



³ Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2019 (GBD 2019) Reference

Life Table. Seattle, United States of America: Institute for Health Metrics and Evaluation (IHME), 2021.

⁴ Lopez-Otin et al. "The Hallmarks of Aging." Cell.



THE NINE HALLMARKS OF AGING

Cell senescence is one hallmark of aging currently attracting a lot of scientific attention. Cell senescence denotes a biological condition in which cells lose the ability to divide, but continue to circulate in the body in a zombie-like state. Early in life, new cell creation outpaces cell senescence. However, as you age, senescent cells accumulate, leading to inflammation. Cellular senescence is involved in a range of age-related diseases including diabetes and osteoarthritis. Research suggests the removal of senescent cells provides therapeutic benefits.

Two other hallmarks of aging attracting significant research are altered intercellular communication and mitochondrial dysfunction. Your cells must be able to communicate with one another for your body to function. They use an intricate network of chemical signaling molecules to communicate. As you age, this vast communication network suffers signal degradation. The signals weaken and communications run haywire. Mitochondrial dysfunction happens when your mitochondria – which produce 90% of the human body's energy – are disrupted. Fewer mitochondria are made as you age, meaning that those that remain must work harder, potentially leading to issues caused by over-metabolization. Loss of mitochondrial function can also lead to fatigue, a common symptom of aging.

Besides the three described above, there are six additional hallmarks of aging: (1) genomic instability, the accumulation of genetic damage over the course of a lifetime; (2) telomere attrition, the degradation of protective DNA at the end of the chromosome; (3) epigenetic alterations, which can negatively impact the way your DNA is processed; (4) deregulated nutrient sensing, which affects how your body metabolizes nutrients to release energy; (5) stem cell exhaustion, in which your body is no longer able to replace dying cells fast enough to maintain peak function; (6) loss of proteostasis, which involves the misshapening and dysfunctioning of crucial proteins.



Research supported by the National Institute on Aging suggests these nine hallmarks of aging interact in layered and nuanced ways. The NIA has launched several new funding initiatives to investigate how the hallmarks interact and whether they should be targeted for interventions individually or in groups. Supporting this and similar research will be critical to further our understanding of the biological mechanisms of aging and how to treat it.

The Longevity Industry: History, Current State of Play, & Next-Gen Technologies

Medical research has been centered around a disease-based approach – targeting one disease at a time, without addressing aging as an underlying cause. While NIH funded aging research as far back as 1940, NIA first sponsored research examining basic aging biology in 1975.⁵ Overall, investments into medicines targeting healthspan holistically, preventatively, and/or systematically was limited and slow to develop prior to 2010.

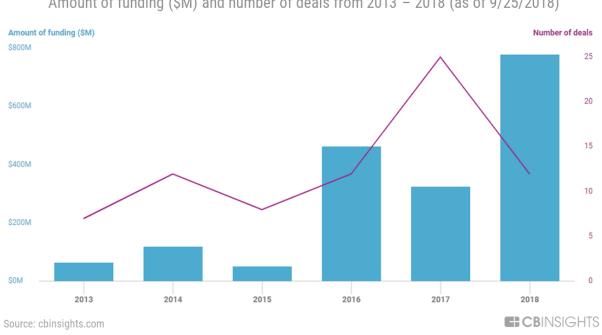
Similar to public sector sponsorship, private sector funding for aging research has been sparse. There are myriad regulatory and reimbursement barriers to developing therapies to treat aging. Many of these barriers stem from outmoded 20th century drug development and insurance models.

Until recently, the barriers limited pharmaceutical companies' interest in longevity therapies, though a few biotechnology companies have had success. In 1990, some companies had already launched to develop longevity therapies. Early forerunners typically focused on developing small molecule pharmaceuticals to target the cellular pathways regulating aging, and then testing those drugs to FDA recognized indications that were "age-related." Such a commercialization strategy arose out of necessity because - at the time of writing - there does not exist a clearly defined regulatory pathway for longevity therapies.⁶



⁵ "International Investment in Geroscience." Public Policy & Aging Report.

⁶ Ibid.

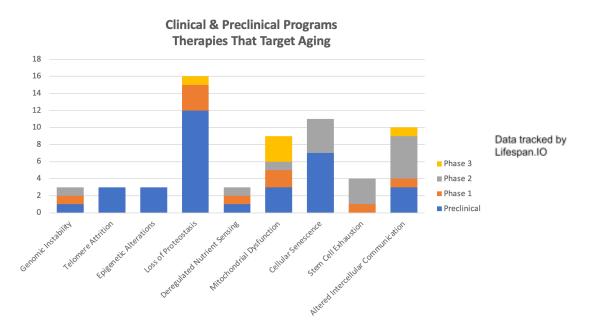


Funding to longevity startups sees a huge jump

Amount of funding (\$M) and number of deals from 2013 – 2018 (as of 9/25/2018)

Over the past ten years, the number of longevity biotech companies has grown significantly. Globally, there are over 171 active "longevity" biotech companies; 63% of them are headquartered here in the US. While most programs are still in their preclinical stage, some have progressed further into the clinical stage. Lifespan.IO is tracking 62 preclinical and clinical programs investigating therapies that target the nine hallmarks of aging, five have reached Phase 3 trials.





Plasmapheresis is one technology that could treat aging. In 2005, a Stanford study led by the Conboys, who now run a lab at the University of California Berkeley, showed that joining the circulatory systems of young and old mice together in a procedure called parabiosis could rejuvenate aged tissues and reverse some aspects of aging in old mice. However, researchers had not yet determined if this effect was due to there being something beneficial in the young blood, or if it was the result of the dilution of harmful factors present in old blood.

A more recent study, released in 2020, suggests the latter: by replacing half of the blood plasma in old mice with a saline and albumin mixture, the albumin replacing the lost protein that was removed when the original old blood plasma was taken, they could achieve a similar or even greater rejuvenation effect in brain, liver, and muscle tissues as joining two mice together through parabiosis. Plasmapheresis is already approved by the FDA for treating a variety of autoimmune diseases, and the research team is currently finalizing clinical trials to determine if a modified plasma exchange in humans could be used to improve the overall health of older people and to treat age-associated diseases that include muscle wasting, neurodegeneration, Type 2 diabetes and immune deregulation.⁷

Current trials are examining several classes of promising therapies. One of the most significant pioneer programs is the Targeting Aging with Metformin (TAME) Trial, a series of nationwide, six-year clinical trials at 14 leading research institutions across the country that will engage over 3,000 individuals between the ages of 65-79. Metformin is a drug that's been approved by the FDA for over 60 years to treat diabetes. Studies have already shown that metformin can delay aging in animals. It may also influence fundamental aging factors that underlie multiple age-related conditions in humans. TAME is testing whether patients taking metformin experience



⁷ "Diluting blood plasma rejuvenates tissue, reverses aging in mice." Berkeley News.

delayed development or progression of age-related chronic diseases, such as heart disease, cancer, and dementia.

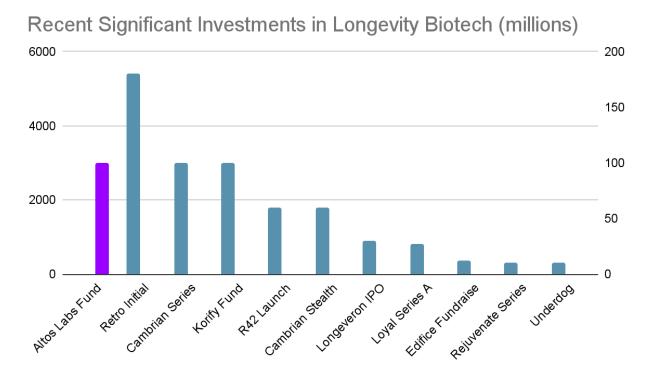
Another class of potential therapies are senolytics. These therapies target senescent cells. Senescent cells exist in a zombie-like state: they no longer produce new cells but linger in the body. They accumulate in tissues throughout the body and secrete factors that damage other cells. They are linked to aging conditions such as frailty and cognitive impairment. Several clinical trials are under way to determine whether senolytic agents developed at the Mayo Clinic, a leader in senolytics, will prevent or even reverse aging. Preliminary research is auspicious: one study (without a placebo control) suggests a senolytic drug alleviates frailty in elderly individuals with serious lung disease.⁸

Active studies are also investigating cellular reprogramming as means of targeting aging. The process is intended to rejuvenate aging cells. While completely reprogramming a cell creates a certain type of stem cell, researchers are generally aiming for "partial reprogramming." Partial reprogramming turns an old muscle cell or a neuron into a younger version of itself. Early studies are encouraging, and although the technology is not yet being tested in humans, several companies plan to bring this technology to the clinic soon: NewLimit announced a \$105 million investment in December 2021 to develop therapies that extend healthspan through epigenetic reprogramming, Retro Biosciences announced \$180 million in initial funding, and Altos Labs launched with \$3 billion in funding to support cellular rejuvenation programming to restore cell health and reverse disease, injury, and disabilities.

The number of therapies under development is likely to grow alongside increased investment activity in this space, with a number of investors and investment funds established in recent years to fund healthspan targeting therapies. These funds include big names such as The Longevity Fund, Y Combinator, ARCH Venture Partners, Khosla Ventures, and others. Private foundations also have a long history of support for this field, including the American Federation for Aging Research, the Salk Institute for Biological Studies, and the Buck Institute for Research on Aging.



⁸"Can You Fight Aging? Scientists Are Testing Drugs to Help." Wall Street Journal.



In addition to investment activity, larger pharmaceutical companies are entering the space. For example, Novartis has dipped its toe into longevity research through its investigations of rapamycin, an immunosuppressant originally approved by the FDA in 1990 to prevent rejection following solid organ transplants. Scientists later found that the drug affects a multitude of biological processes. It has been found to extend the lifespan of yeast, worms, and mice. While there is currently no feasible regulatory pathway to test rapamycin's potential to slow human aging, researchers are examining whether drugs mimicking rapamycin can enhance the elderly diminished immune function. Novartis later spun out a biotech start-up focused on this research.

Overall, the longevity field is growing rapidly. Investment is expanding. Significant scientific and clinical progress has already been made. Longevity medicine has the potential to revolutionize healthcare and dramatically increase the number of years Americans spend in good health. Now, policymakers must help translate these breakthroughs into new medicines that will positively transform society as a whole.



Arguments for Developing Aging Therapeutics

Summary

The development of longevity therapies likely possesses broad bipartisan support. In a January 2022 poll by the Alliance for Longevity Initiatives, 74% of Democrats and 62% of Republicans reported they would utilize longevity therapies. Additionally, the poll found that Democrats (79%) and Republicans (59%) support research into cellular aging.

One straightforward argument in support of political action for aging therapies is predicated on the government's existing role in fighting age-related diseases such as Alzheimer's and cancer. If the government is justified in fighting these diseases, then why shouldn't it be involved in stopping aging itself? The case is made all the more salient by the fact that such efforts will likely produce clues to solving age-related diseases. However, there are several other arguments worth considering. If these arguments were well-known and understood, support for these therapies would likely be even higher. In this section, the guide discusses the moral, financial, and geopolitical arguments for political action to facilitate the development of longevity therapies. The section also addresses common arguments against this field.

Moral Imperative

Developing and commercializing longevity therapies is perhaps the most important thing the U.S. government can do to increase equity and stability among its citizenry. The creation of healthspan impacting medicines will protect society's most vulnerable citizens (seniors) while decreasing disparities in healthcare outcomes between various groups in society.

Aging is the primary underlying risk factor in many of society's most tragic diseases: the risk of cancer, diabetes, heart disease, Alzheimer's, climbs rapidly as we age. As the U.S. population grows older (by 2035, the U.S. will have more elderly individuals than children), it's more important than ever to ensure Americans are able to stay healthy and vibrant as they age.

Approximately 85% of adults over the age of 65 now have at least one chronic disease such as cancer, diabetes, heart disease, stroke, or Alzheimer's disease.⁹ Even more concerning is the proportion of adults with multimorbidity, the coexistence of two or more chronic conditions. Multimorbidity often leads to exacerbated poor health outcomes and a higher risk of premature death. Half of chronically ill patients under the age of 65 were found to experience multimorbidity, compared to 62% for those aged 65-74 years and 81.5% for those 85 years and older.¹⁰ Related to morbidity, about 41% of Americans over 65 have issues performing at least

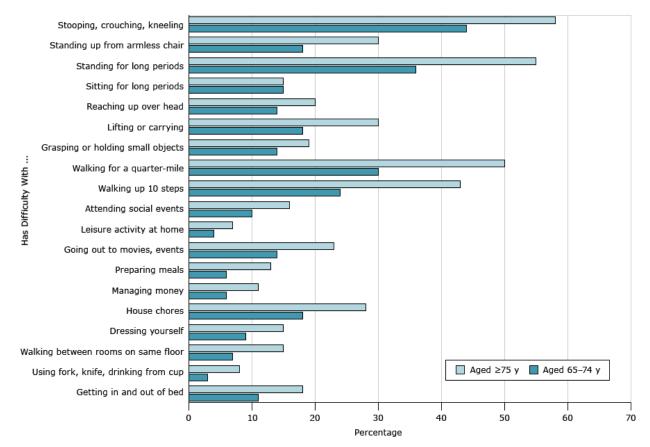


⁹ "Supporting Older Patients with Chronic Conditions." National Institute on Aging.

¹⁰ https://pubmed.ncbi.nlm.nih.gov/23372025/

one activity of daily life (ADLs) such as walking, bathing, dressing and grooming, or feeding oneself.¹¹ Limitations in ADLs are associated with lower quality of life as measured by number of unhealthy days, social functioning, and emotional wellbeing.¹²

The number of people ages 65 and older in the United States has increased steadily since the 1960s, but is projected to more than double from 46 million today to more than 98 million by 2060. Between 2020 and 2030 alone, the number of older persons is projected to increase by almost 18 million as the last of the large baby boomer cohorts reaches age 65. Although much smaller in total size, the number of people ages 85 and older is projected to more than triple from 6 million today to nearly 20 million by 2060.¹³ As a group, the baby boomer generation also has higher rates of obesity and mobility-related impairments.



Furthermore, the pool of traditional family caregivers for older Americans is shrinking as marriage and fertility rates decline and divorce rates increase. More adults will reach age 65 without a spouse or adult child to rely on for care. This caregiver shortage compounds the need to ensure older adults are healthy enough to function independently. In order to accommodate the needs of an aging population and ensure older U.S. adults are able to maintain good health and



¹¹ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5360539/

¹² https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3593634/#R15

¹³ "Population Bulletin." Population reference Bureau.

functional independence as they age, it is imperative that the U.S. government do all it can to promote advances in the field. Due to high levels of comorbidity, addressing the underlying cause of these diseases – the biological hallmarks of aging – is the most feasible strategy to do so.

Additionally, longevity therapies have the potential to address significant racial and socioeconomic disparities in the health of older adults. While these disparities exist across the spectrum of aging, they are particularly significant among the older population, and the COVID-19 pandemic has further magnified these disparities. The Hispanic population experienced the largest drop in life expectancy during the COVID-19 pandemic, falling by three years over the course of 2020 alone. Life expectancy for the non-Hispanic black population decreased by almost as much at 2.9 years.¹⁴ Income also plays a significant role in life expectancy. From 2001 to 2014, the richest Americans gained approximately 3 years in longevity – an effect equivalent to the effect that curing cancer would have on life expectancy – but the poorest Americans experienced no gains. And Americans among the top 1% for household income live on average 15 years longer for men and 10 years longer for women than Americans in the bottom 1%.¹⁵

The disabling effects of aging are also more likely to affect older adults of color, who are at a higher risk of having low physical capacity, poor vision, and dementia. They are also more likely to experience unmet needs related to self-care, mobility, and household activities.¹⁶ Additionally, older adults without a high school diploma are more likely to experience poor health outcomes and have shorter lifespans than adults with a college degree.¹⁷ Nearly 15% of older Americans live below the poverty threshold, putting them at increased risk of decline in mental health and the development of dementia.¹⁸ And once diagnosed, low-income patients may receive lower quality care: one study showed that low-income Alzheimer's patients were significantly less likely to have received specialist care within the past year.¹⁹

In addition to reduced quality of life for the patients suffering from these poor outcomes, care for disabled parents can create a significant financial burden on low-income caregivers. Low-income caregivers tend to provide parental care with limited economic resources and options. This may increase their financial burden due to lost wages from reduced work hours, family leave, or early retirement. In this sense, low-income caregivers often experience a vicious cycle of increased

¹⁹ https://twin-cities.umn.edu/news-events/obtaining-specialist-care-may-be-harder-rural-and-lower-income-alzheimers-patients



¹⁴ https://www.cdc.gov/nchs/pressroom/nchs_press_releases/2021/202107.htm

¹⁵ http://www.equality-of-opportunity.org/health/

¹⁶ https://news.umich.edu/older-americans-are-aging-better-than-ever-especially-women/

¹⁷ https://www.prb.org/resources/eight-demographic-trends-transforming-americas-older-population/

¹⁸ https://www.apa.org/pi/ses/resources/publications/age

negative outcomes.²⁰ There is also a significant psychological effect: for example, low-income caregivers of dementia patients have been found to be at higher risk of depression.²¹

Longevity therapies could help to offset the disproportionately poor health outcomes experienced by older adults of color and adults living beneath the poverty line. These therapies could treat or even prevent negative conditions such as cancer, diabetes, heart disease, stroke, or Alzheimer's disease. By addressing age-related diseases, longevity medicines could help to ensure people of color and those living beneath the poverty line in the U.S. age more equitably. Addressing disparities in health and health care is not only just and equitable, it's also important for improving the nation's overall health and economic prosperity. As the population becomes more diverse, with people of color projected to account for over half of the population by 2050, it is increasingly important to address disparities.

The government's responsibility to protect and advance the interests of society includes the delivery of high-quality health care. Current policies severely limit the private sector's ability to develop and deliver therapies targeting healthspan. The government must preserve its citizens' interests by implementing policies more conducive to the development of these therapies, promote research into the underlying causes of aging, and addressing inequalities in health outcomes for the United States' aging population.

Economic Motivation

Having a healthier, longer lived population would allow our workforce to be smarter and more productive. By implementing policies more conducive to the creation of healthspan impacting medicines, less people would be chronically ill moving forward and that would result in massive savings across society. The longevity dividend economic argument states that by promoting healthy aging and making getting older a net positive on society (not net negative as it is now) we can achieve unprecedented economic growth.

By treating the underlying cause of age-related diseases and ensuring older Americans avoid the diseases associated with aging (cancer, Alzheimer's, heart disease, diabetes) and disabling conditions of aging, (weakened immune function, arthritis, loss of muscle) the United States stands to establish significant financial benefits. The government pays for more than 65% of healthcare costs for the ederly through Medicare and Medicaid spending. This includes \$281 billion spent annually on heart disease;²² \$206 billion on Alzheimer's disease;²³ \$183 billion on

²³ "Costs of Alzheimer's to Medicare and Medicaid." Azheimer's Impact Movement: Alzheimer's Association (2020). https://act.alz.org/site/DocServer/2012_Costs_Fact_Sheet_version_2.pdf?docID=7161



²⁰ https://academic.oup.com/psychsocgerontology/article/70/3/425/544816?login=true

²¹ https://journals.sagepub.com/doi/full/10.1177/0046958017750432

²²https://www.cms.gov/Research-Statistics-Data-and-Systems/Research/MCBS/Downloads/HeartConditions_DataBr ief_2017.pdf

cancer;²⁴ and \$176 billion on diabetes.²⁵ With the average age of the population increasing, these costs could grow exponentially in coming years.

Additionally, other complications of aging – including weakened immune function, physical frailty, and physical disability – also contribute to significant medical costs covered by government programs. Declining immune function played a significant role in the disproportionate impact the COVID-19 pandemic had on older adults; this was a large driver in the approximately \$400 billion increase in national healthcare spending in the United States from 2019 to 2020.²⁶ And the cost of the pandemic has continued to mount in the two years since.

Physical disability also presents a significant financial burden to the United States. About 41% of Americans aged 65 or older now have issues performing at least one limitation in performing activities of daily life (ADLs) such as walking, bathing, dressing and grooming, or feeding oneself,²⁷ often resulting in the need for long-term care services such as in-home nursing or assisted living facilities. Nursing home expenses are a significant concern for the elderly, with costs on the order of \$77,000 to \$88,000 a year.²⁸ Long term care services cost the government \$136 billion in 2020.²⁹

By addressing the underlying causes of age-related disease, the United States could see significant financial returns. The sources of these returns are multifold. The healthcare system is no longer paying to treat the symptoms of chronic disease. Families are no longer forced to pay for assisted living facilities, or give up on their own potential earnings to become full time caregivers. The government would also experience significant savings from decreased use of assisted living facilities. Older adults would need fewer interventions to accommodate disabilities such as reduced mobility, poor vision, and poor healing. Older adults could work longer, improving their economic productivity. The increase in average lifespan would mean that older adults would be participating in the economy in other ways – traveling, buying groceries, seeing the movies, and such – for longer. And these savings would be further magnified as the United States is able to reinvest this money into more fruitful endeavors.

The savings add up to what is known as the Longevity Dividend. The American Federation for Aging Research estimates that by delaying or preventing chronic age-related diseases, adding just 2.2 years of healthy life to the average American's lifespan, the United States could save



²⁴ https://jamanetwork.com/journals/jama/article-abstract/2785966

²⁵https://www.cms.gov/Research-Statistics-Data-and-Systems/Research/MCBS/Data-Briefs-Items/Diabetes_DataBri ef_2017

²⁶https://www.cms.gov/newsroom/press-releases/national-health-spending-2020-increases-due-impact-covid-19-pan demic

²⁷ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5360539/

²⁸ "<u>Medical Spending of the Elderly.</u>" National Bureau of Economic Research.

²⁹ how much does medicaid spend on long term care

\$7.1 trillion.³⁰ This is a conservative estimate. Others suggest the return could be as high as \$38 trillion for just one added year.³¹

The longevity dividend relies heavily on researchers' abilities to not only increase lifespan, but healthspan as well. While the estimated value of one additional year of life for the average American is \$118,000, the value of one year of *healthy* life more than doubles to \$242,000.³² This is because in order to reap the significant financial benefits of increased average productivity, workers must not only live longer, but do so with the physical and mental capacity to remain productive.

The goal for policymakers, then, should be to achieve healthy aging. Aging can be affected in four ways, known as forms of aging malleability: behavioral factors (such as diet and exercise), environmental factors (such as clean air and water), socioeconomic factors (addressing racial and economic disparities in health outcomes), and biological (addressing the underlying biological causes of aging). While all four forms of aging play a role, however, addressing the biological causes of aging is most likely to have the largest impact on increasing healthy lifespan. For example, even older adults who engaged in healthy eating and exercise habits were still at risk of increased mortality due to the COVID-19 pandemic. That is because, under the current standard of care, many of the physiological effects of aging, such as decreased immune function, are immutable. Longevity therapies, however, could offset the negative effects of addressing these biological aspects of aging, this form of age malleability receives the least attention from policymakers.³³

The U.S. national debt has exceeded \$30 trillion for the first time in the nation's history. Nearly 80% of Americans say they worry about the federal budget deficit either a great deal or a fair amount.³⁴ The biggest drivers on the spending side are the aging of the population and health care costs. Those two things have caused growth in the United States' biggest programs – Medicare, and Medicaid – and they are eclipsing economic growth. Significant innovation is needed in order to cut healthcare costs. Policymakers are already beginning to recognize the significant potential that longevity medicines present to address this issue. In an op-ed, former Speaker of the House Newt Gingrich described aging research as key to balancing the budget. It is vital that the United States prioritize the development of therapies in order to offset healthcare costs and drive economic growth in the 21st century.³⁵



³⁰ https://www.afar.org/learn

³¹ https://www.nature.com/articles/s43587-021-00080-0

³² https://www.sci-hub.wf/https://www.nature.com/articles/s43587-021-00074-y

³³ https://www.sci-hub.wf/https://www.nature.com/articles/s43587-021-00074-y

³⁴ https://news.gallup.com/poll/147626/federal-budget-deficit.aspx

³⁵ https://a4li.org/2022/02/newt-gingrich-aging-research-is-key-to-balancing-the-budget/

Geopolitical Motivations

The United States is not the only country with an aging population. Japan is, on average, the oldest country in the world: 28.7% of the population is over age 65, and by 2036, people aged 65 and older could represent one third of the population.³⁶ The older population in China is also growing; while only 18.7% of China's current population is age 60 or older,³⁷ that number could be 28% by 2040.³⁸ This trend holds true for Europe as well – the share of people aged 65 and older in the EU is expected to rise from 19% to 29% of the population, and people aged 80 and over will increase from 5% to 13% by 2070.³⁹

An aging population poses great risk to public policy and affairs: all else even, a lower labor participation rate results in less tax revenue for the government. On top of this, more elderly means more resources required to fund retirement programs, healthcare, and assisted living costs. Therefore, insofar as they curtail risks posed by our nation's aging population, longevity therapies should be one of our highest priorities.

Across several metrics, the United States is the world's largest biotech hub. However, other regions – particularly China – are gaining ground. Some estimates claim that collectively, China's central, local, and provincial governments have invested over \$100 billion in life sciences research and development.⁴⁰ In biomedical patents, China's annual growth rate of 16% far exceeds America's 3%, and in novel cell therapy patents China leads in both total patents and growth rate.⁴¹ If the United States does not take steps now to facilitate the development of longevity therapies, it's likely the United States will lose ground to China.



³⁶ https://www.europarl.europa.eu/RegData/etudes/BRIE/2020/659419/EPRS_BRI(2020)659419_EN.pdf

³⁷https://www.scmp.com/economy/china-economy/article/3157385/chinas-ageing-population-long-term-reality-and-its-silver

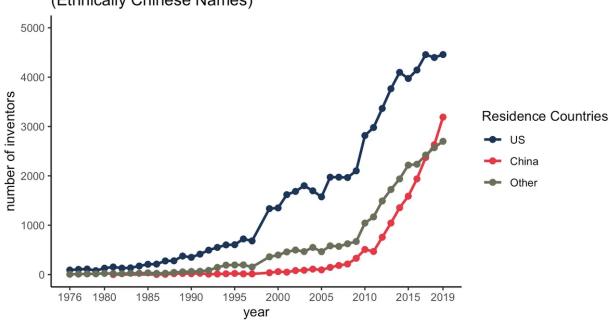
³⁸ https://www.who.int/china/health-topics/ageing

³⁹ https://www.icf.com/insights/social-programs/aging-population-in-europe

⁴⁰ https://www.brookings.edu/wp-content/uploads/2020/04/FP_20200427_china_biotechnology_moore.pdf

⁴¹ John Wong, Chun Wu, Wen Xie, and Srikant Vaidyanathan, "Competing in China's Booming Biopharma Market," BCG,

November 12, 2020, https://www.bcg.com/publications/2020/competing-in-chinas-biopharma-market.



Chinese Inventors of U.S. Biotech Patents, by Residence Countries (Ethnically Chinese Names)

In addition to direct competition, the financial benefits of longevity therapies discussed in the previous section will also benefit those countries that invest and secure supremacy in the longevity field. China's economy is already set to potentially overtake the U.S. economy by 2030.⁴² This could be further exacerbated if China reaps the financial benefits of increased longevity while the United States does not. In order to continue to compete with countries like China in the global economy, it is vital that the United States remains dominant in this field.

Longevity medicines will also translate into significant competitive advantages as well: longevity therapies should improve the labor force. If the average person is living longer in good health, they're also likely to participate in the workforce for longer, increasing the experience level of the average worker.

This benefit extends beyond the private sector. It also ensures U.S. service men and women are in better health, stronger and more mentally sharp than the country's adversaries. Additionally, ensuring high-performing members of the military are in better health means benefitting from their expertise for longer. Veterans are at an increased risk for many age-related diseases, including Alzheimer's disease, Parkinson's disease, and cancer. Longevity therapies could be specifically beneficial to both active and former members of the U.S. military.⁴³



⁴² https://www.voanews.com/a/chinas-economy-could-overtake-us-economy-by-2030/6380892.html

⁴³ "<u>10 Common Medical Issues in Veterans.</u>" UnityPoint Health.

Debunking Arguments Against Longevity Science

Overpopulation⁴⁴

When discussing longevity science, the possibility of global overpopulation is often broached. The argument is that medical advances that increase lifespan by addressing the underlying biological causes of aging could contribute to an overpopulated world. The first counterargument to this is that even if overpopulation was a concern, people have a moral right to live, and it's repugnant to expect them to die simply to make room for additional people. This begs the question: is overpopulation even that much of a concern to start with?

Since the 1960s, both birth rate and population growth have been gradually falling. The world population will likely level off at 11 billion people near the year 2100. It's unlikely that the world will run out of space: if all humans lived in cities with the approximate population density of New York City, for example, 11 billion people could fit in an area the size of just three U.S. states – Louisiana, Texas, and New Mexico. Additionally, advances in agriculture have meant that world hunger continues to drop, despite recent increases in the overall population.

This suggests that the traditional concerns of overpopulation – running out of space and resources – should not be the main concern. Instead, what policymakers should be worried about is the age structure of the population. Societies need enough people of working age to produce goods and services, pay taxes, and support non-working groups – primarily children and the elderly. Right now, as the global population increases, many countries are facing the challenges of an aging population that requires more resources, including increased healthcare expenditures and more working age people required to act as caregivers for disabled older adults.

In this case, research into longevity therapies are actually a part of the solution rather than the problem, by ensuring the elderly population is healthier for longer and reducing the resources needed to care for them.

Potential for economic disparities

Another concern is that novel therapies may only be accessible by the rich. However, new medical technologies typically become cheaper over time, so high costs will not be a permanent barrier. Additionally, recent breakthrough therapies with record breaking prices – for example, Novartis's gene therapy for spinal muscular atrophy, priced at over \$2 million – are typically targeting rare diseases, so research and development costs are not shared over a large patient population. By contrast, millions of people worldwide are at risk to develop age-related diseases – meaning that the per-patient cost is expected to be much lower.



^{44 &}quot;Increased Longevity and Overpopulation" Lifespan.io

Additionally, governments are already paying exorbitant costs to support multiple health interventions for older people suffering from age-related diseases. Therefore, it is likely that governments will be able to subsidize the cost of longevity therapies while still experiencing net savings from an overall healthier population, leading to lower medical costs and increased economic productivity.

Longer lifespans are unnatural

Just because something is "unnatural" – in this case meaning it's made or caused by humankind – does not mean that it's a bad thing. All of modern healthcare could be described as unnatural, but that does not stop society from enjoying the benefits of vaccines, antibiotics, and surgeries. Outside of the healthcare realm, modern amenities such as computers, indoor plumbing, heating and air conditioning, and others could also be described as unnatural.

Furthermore, there is an argument to be made that extended lifespans are, in fact, natural. There are species in the natural world that can live over five hundred years, and some do not appear to age – meaning they show no increased risk of dying as they get older. Evolution has already created natural examples of extended lifespan.

People should focus on living better, not longer

If you ask a person how they would prefer to die, most will tell you they would like to go peacefully in their sleep rather than experiencing a drawn-out decline in health. Is living longer really worth it if it just means being sicker for longer?

This argument represents a misunderstanding of the core of longevity research. There isn't a natural dichotomy between living longer and remaining healthy. By targeting the underlying causes of aging, scientists will actually be able to treat age-related diseases such as Alzheimer's, diabetes, cancer, and others, and prevent the loss of muscle tone, immune function, mobility, vision, and hearing in old age. The biggest gains the longevity sector will see will be in healthspan – the part of a person's life during which they are generally in good health – not just lifespan. Simply put, this area of science will allow Americans to live both better and longer.

Pensions and healthcare costs will become unsustainable

As mentioned previously, longevity therapies would actually help to decrease healthcare expenditures. Additionally, the retirement age could potentially be raised to reflect increases in later-life productivity, and increases in economic productivity – and therefore tax revenue – could help to offset the cost of programs like Social Security. Therefore, it is likely that these therapies would actually improve the economy. The American Federation for Aging Research estimates that by delaying or preventing chronic age-related diseases, adding just 2.2 years of healthy life to the average American's lifespan, the United States could save \$7.1 trillion over the



next 50 years.⁴⁵ This is a conservative estimate. Others suggest the return could be as high as \$38 trillion for just one added year.⁴⁶

The future isn't worth living for

Some people are concerned that the future of the world will be unpleasant for those who experience it. They may be opposed to the extension of lifespan (which is a side effect of increasing healthspan) because they are under the impression that the future isn't worth living for. However, by most objective measures, the world has been on a clear, positive trajectory. The world is experiencing lower poverty and hunger, more recreation time, less violence, improved education, improved health outcomes, faster travel and communication, and a wealth of technological advances. And economic gains from increased longevity could be re-invested to continue these trends.

Living longer means lower job turnover

As people age, they eventually retire and leave the workforce, creating job openings for the next generation. If people live longer, will that mean there are fewer job opportunities available for young people? That scenario is unlikely because of the economic gains created when the average lifespan is elongated. Living longer means an increased demand for goods and services that will fuel job creation.

Will dictators live longer?⁴⁷

Some opponents argue longevity therapies will prolong the lives of dictators. However, addressing this problem by halting the development of therapies that could drastically improve the lives of billions of people worldwide is a net negative. No one would argue that researchers should stop developing medicines for cancer or heart disease patients because those therapies could be used to extend the lives of evil people. In addition, even if the aim is to ensure dictators die earlier due to developing age-related diseases, a positive outcome is far from assured, as in many cases another dictator will take the place of the deceased.

Additionally, there is a worldwide trend towards fewer dictators and a smaller proportion of the population living under autocratic governments. It is likely that, regardless of the development of longevity therapies, this will become less of an issue over time.

Will people become bored if they live "too long"?⁴⁸

It's unlikely that anyone will become so bored that age-related decline and eventual death is preferable. This is especially true given that better health in old age means that older Americans will be able to work longer, travel more, maintain interpersonal relationships, and pursue hobbies



⁴⁵ https://www.afar.org/learn

⁴⁶ https://www.nature.com/articles/s43587-021-00080-0

⁴⁷ "Increased Longevity and Immortal Dictators" Lifespan.io

⁴⁸ "<u>Would Increased Longevity be Boring</u>?" Lifespan.io

and recreational activities more easily. Therefore, these therapies are likely to decrease boredom experienced by older adults. In cases where an individual feels that they are no longer receiving personal satisfaction from living longer, they would be free to discontinue treatment to prolong their lifespan.

How Can Policymakers Help?

Summary

For the first time in history, it appears aging is not an inevitable fate to which every human is consigned. Recent scientific advances demonstrate that the underlying causes of aging can be treated to prevent age-related diseases, ensuring Americans live longer, healthier lives. Supporting this kind of medicine is not only a morally imperative – it's a fiscally and politically sound investment. So what actions can the government take to advance the field?

A4LI has identified five actions Congress can take:

- 1. Increase allocations to the National Institute of Aging Division of Aging Biology;
- 2. Make geroscience and longevity medicine a focus of ARPA-H;
- 3. Create a dedicated regulatory pathway for longevity medicines;
- 4. Fund Congressional Budget Office research into the longevity dividend; and
- 5. Initiate a national movement to increase healthy lifespan by setting an actionable, time-bound goal.

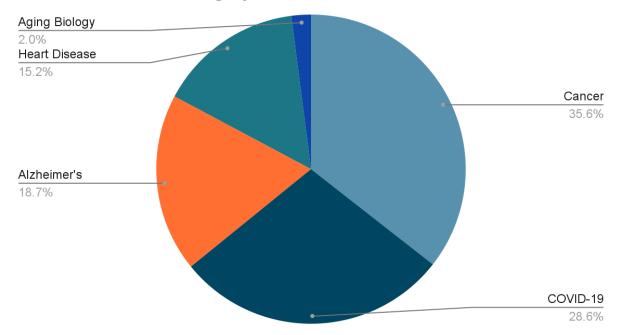
In this section, the guide explains these legislative actions and how they will move the dial on the health of all Americans.

1. Increase Allocations to the National Institute of Aging – Division of Aging Biology

Aging research in the United States is severely underfunded. Just 0.6% of the budget for the National Institutes of Health – \$350 million of the nearly \$52 billion budget – is spent on research into aging biology. In comparison, cancer receives \$6.1 billion in research funding; COVID-19 receives \$4.9 billion; and heart disease receives \$2.6 billion.⁴⁹ Even the National Institute of Aging within the NIH spends just 10 percent of its budget on the biology of aging. Most of its funding is spent on neuroscience – in particular, research into Alzheimer's disease and dementia.



⁴⁹ https://report.nih.gov/funding/categorical-spending#/



NIH Research Funding by Disease

Callout graphic: NIH Research Funding by Indication

- Cancer: \$6.1 billion
- COVID-19: \$4.9 billion
- Alzheimer's: \$3.2 billion
- Heart disease: \$2.6 billion
- Aging biology: \$350 million

Increasing funding for aging biology research is vital, because aging is the leading risk factor for each of these diseases. Take cancer, for example. President Biden recently announced that the White House will reinvigorate Cancer Moonshot: reduce the death rate from cancer by at least 50 percent over the next 25 years, and improve the experience of people living with cancer.⁵⁰ Funding aging research may be the most effective way to achieve these goals. Consider that, while smoking increases your risk for cancer by a factor of 15, aging increases it by 100. Any comprehensive research into cancer prevention will require a better understanding of the aging biology underlying this risk factor.

Furthermore, funding this research will not only develop strategies for cancer prevention. The same research will create in-roads for preventing other age-related diseases including diabetes, heart disease, and Alzheimer's disease. That's why every dollar spent on aging biology research is like spending a dollar for research on *every single age-related disease*.

⁵⁰https://www.whitehouse.gov/briefing-room/statements-releases/2022/02/02/fact-sheet-president-biden-reignites-ca ncer-moonshot-to-end-cancer-as-we-know-it/



Given the benefits that such research will have on health outcomes for a wide variety of diseases, it is vital that the U.S. prioritizes funding for this field. A4LI calls for Congress to treble the budget of the National Institute of Aging – Division of Aging Biology to \$1 billion by 2025.

2. Make geroscience and longevity medicine a focus of ARPA-H

To accelerate research that can improve Americans' health, President Biden is proposing the establishment of the Advanced Research Projects Agency for Health (ARPA-H). Included in the President's FY2022 budget as a component of the NIH with a requested funding level of \$6.5B available for three years, ARPA-H will be tasked with developing high-risk, high-reward technologies to drive biomedical breakthroughs – ranging from molecular to societal – that would provide our nation's patients with transformative solutions. The program is modeled after the extremely successful Defense Advanced Research Projects Agency (DARPA), which is responsible for technological advancements such as the computer mouse and "packet-switching" – the foundation for today's internet.

ARPA-H would help to fund bold ideas that slip through current cracks in research and development because:

- the risk is too high;
- the cost is too large;
- the time frame is too long;
- the focus is too applied for academia;
- there is a need for complex coordination among multiple parties;
- the near-term market opportunity is too small to justify commercial investment; and/or
- the scope is so broad that no company can capture the economic benefit.⁵¹

Research into longevity therapies meets several of these qualifiers. Drug development is always commercially risky. However, it is especially risky when exploring a new class of medicines predicated on novel underlying biology. Designing clinical trials to test interventions that target the aging process poses a unique set of challenges – for example, testing the effect on longevity itself may not be feasible in the time frame of a typical clinical trial – which can further increase costs and risks. Because of these aspects of aging research, it is particularly suited for ARPA-H.

A key factor in DARPA's success is the role of program managers. They work with R&D stakeholders to establish rigorous, aggressive program goals (including detailed technical milestones) needed to manage a portfolio of sophisticated R&D projects. For ARPA-H to succeed in its mission, program managers must have an understanding of the geroscience approach and the potential impact longevity medicine will have on society.



⁵¹ https://www.whitehouse.gov/wp-content/uploads/2021/09/092921-ARPA-H-FAQ.pdf

Like DARPA, ARPA-H should be solely focused on making pivotal investments in next-generation, breakthrough medical technologies. Geroscience has the ability to simultaneously treat many of the diseases Americans face in later life, and should be given high priority as ARPA-H is established. Given these parameters, A4LI supports the establishment and appropriate funding of ARPA-H, and urges policymakers to make geroscience a priority as the program moves forward.

3. Create a dedicated regulatory pathway for longevity medicines

In 2016, Congress passed the 21st Century Cures Act, intended to accelerate medical product development and commercialization. The Cures Act established a new expedited product development program, the Regenerative Medicine Advanced Therapy (RMAT) Designation.

This designation, intended to expedite the approval of cell, gene, and tissue-based products, can be granted for products that are intended to treat a serious disease and have shown preliminary clinical evidence indicating the drug has the potential to address unmet medical needs. Benefits of the designation include increased FDA interaction and eligibility to apply for priority review for approval of the new therapy.⁵² To date, 68 therapies have received the FDA's RMAT Designation, and three have been approved: one therapy to treat a rare, fatal birth defect, one therapy to treat a serious form of lymphoma, and one therapy to treat severe burns.⁵³ Other therapies that have received the designation target sickle cell disease, fatal genetic disorders, and cancers that no longer respond to chemotherapy.

While there are other FDA Designations that are technology agnostic – the Breakthrough and Fast Track Designations – the RMAT Designation has some advantages over those pathways. For example, while the benefits of the Breakthrough Designation and RMAT Designation are very similar, the RMAT Designation has slightly less strenuous requirements for receiving the designation. This allows the FDA to better incentivize development for this novel class of therapeutics.

The RMAT Designation has catapulted regenerative medicine into the mainstream. A Longevity Medicine (LM) Designation could do the same for longevity therapies. While some aging therapies fall under the category of regenerative medicines, some would not. They will need to meet the stricter requirements of a Breakthrough Designation. Additionally, because aging is not currently recognized as a disease by the FDA, and because many of these therapies would be preventative in nature, it is possible that they may not qualify as intending to treat, modify, or

⁵³https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/cumulative-cber-regenerative-medici ne-advanced-therapy-rmat-designation-requests-received-fiscal



⁵²https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/regenerative-medicine-advanced-the rapy-designation

reverse a serious or life-threatening disease or condition. Instead, sponsors would need to resort to showing that the therapy could treat one specific age-related disease, and then conduct additional trials to expand into other indications.

A4LI calls for the creation of a specialized Longevity Medicine Designation that could be tailored to reflect the unique potential of this class of therapies. This designation could help to create regulatory clarity for aging therapies and accelerate their development.

4. Fund Congressional Budget Office Research into the Longevity Dividend

By addressing the underlying causes of age-related disease, the United States could see significant financial returns. The government pays for more than 65% of healthcare costs for the elderly through Medicare and Medicaid spending.⁵⁴ Age-related diseases pose the most significant financial burden on the American healthcare system. For example, Alzheimer's and other forms of dementia cost the U.S. \$305 billion in 2020, with Medicare and Medicaid paying for roughly \$206 billion of those costs. And with the average age of the American population increasing, those expenses are expected to nearly triple by 2050.⁵⁵

Besides offsetting the direct cost of treating age-related diseases, this field will provide significant indirect financial benefits. The savings will be further amplified when the U.S. reinvests these hundreds of billions of dollars. Additionally, Older adults could work longer, improving their total economic output. Moreover, an increase in average healthspan would mean older adults participate as consumers – traveling, buying groceries, seeing movies – for longer.

As described previously, these economic benefits add up to what is known as the longevity dividend. Economists have previously evaluated the value of increasing the healthy human lifespan; estimates range from \$7.1 trillion in returns for increasing the average healthy human lifespan by 2.2 years,⁵⁶ to \$38 trillion for just one additional year of healthy life.⁵⁷

It is clear that developing aging therapies has financial benefits, but the exact return depends on many factors. There is a need for objective, nonpartisan, and timely analysis of the longevity dividend to inform Congressional actions in this field of science. With many voters and politicians increasingly concerned with the national debt, it is imperative that the United States is able to fully realize the financial benefits of longevity therapies. The Congressional Budget Office is uniquely positioned to provide this analysis. **A4LI urges Congress to ask that the**



⁵⁴ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6680320/

⁵⁵ "Costs of Alzheimer's to Medicare and Medicaid." Azheimer's Impact Movement: Alzheimer's Association (2020). https://act.alz.org/site/DocServer/2012_Costs_Fact_Sheet_version_2.pdf?docID=7161

⁵⁶ https://www.afar.org/learn

⁵⁷ https://www.nature.com/articles/s43587-021-00080-0

CBO conduct research to determine the potential impact of the longevity dividend in the U.S.

5. Initiate a National Movement to Increase Lifespan and Healthy Lifespan

In 2017, the United Kingdom released a white paper identifying four 'grand challenges' designed to tackle significant issues the country is facing. One of those was a grand challenge on aging, championed by the country's All-Party Parliamentary Group on Longevity. Like many other countries, people over 65 are a rapidly growing proportion of the population – potentially leading to lower tax revenue as retirees exit the workforce and an increased strain on national resources. In 2018, the UK set a new goal to propel this 'grand challenge on aging' forward: to add five years to healthy life expectancy by 2035. To help reach this goal, the UK has announced £130 million of investment to support healthcare innovation, including £69.5 million towards new treatments that allow people to lead healthier and longer lives.⁵⁸

The UK is not the first major government to take this approach to extending life expectancy: in 2008, the European Union announced a goal to increase average life expectancy by two years by 2020, a goal they achieved.⁵⁹ This approach has been utilized for other initiatives, including health-related initiatives, in the United States: President Biden's recent Cancer Moonshot aims to cut today's age-adjusted death rate from cancer by at least 50 percent over the next 25 years.⁶⁰ The Department of Health and Human Services' Healthy People program, first established in 1979, outlines clear, measurable goals as a part of a ten-year plan to improve health outcomes in the U.S.⁶¹

These are examples of public longevity goals that are strategic, measurable, attainable, results-oriented, and time-bound (SMART), often used in government and industry. Publicizing them encourages follow through.⁶² To increase the average American's healthspan, policymakers should outline clear, actionable goals that can be supported by both the legislative and executive branches. As such, A4LI encourages Congress to initiate a national movement to increase healthspan by adopting a goal to increase the average American's healthspan by five years by 2030.

⁶²https://www.researchgate.net/publication/321440716_Unique_Effects_of_Setting_Goals_on_Behavior_Change_Sy stematic_Review_and_Meta-Analysis



⁵⁸https://www.gov.uk/government/publications/industrial-strategy-the-grand-challenges/missions#healthy-lives
⁵⁹ https://austriaca.at/0xc1aa5576_0x003bb589.pdf

⁶⁰https://www.whitehouse.gov/briefing-room/statements-releases/2022/02/fact-sheet-president-biden-reignites-ca ncer-moonshot-to-end-cancer-as-we-know-it/

⁶¹ https://health.gov/healthypeople

Conclusion

The longevity field has reached a critical moment. We are developing therapies targeting the underlying causes of aging to treat and prevent diabetes, Alzheimer's, cancer, and age-related loss in muscle and immune function. These therapies have the potential to radically improve health outcomes for older people in the United States, ensuring they live longer, healthier lives. They have the potential to help Americans subsist independently in their older years.

In addition to the moral imperative the U.S. government has to support medicines that will transform their citizens' lives, aging therapies are a sound financial and political investment. Our nation can look forward to reduced healthcare costs and greater economic growth as more citizens participate in the economy for longer. These benefits have the potential not only to offset, but also exceed the therapies' development costs. Additionally, the United States stands to establish a significant competitive advantage over other countries by investing early into longevity therapies. By becoming a leader in the longevity space, the United States can increase its economic output, improve the average experience level of U.S. workers, and improve the health of U.S. servicemen and women.

To fully realize and accelerate the accruement of these benefits, Congress must take action to pave the way for the development of longevity therapies. There is broad bipartisan support for longevity research. As such, policymakers should take this opportunity to represent the interest of all Americans by enacting legislation to advance this transformative new form of medicine. Create a specialized regulatory pathway for longevity medicines. Support Congressional Budget Office research into the longevity dividend. Set actionable, time-bound goals to launch a national movement to increase Americans' healthspan. A4LI looks forward to working with policymakers to advance this innovative field and create social and political action around the issues of combating age-related chronic conditions and increasing Americans' number of healthy, disease-free years.

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