The Future of Longevity

IMPACT ROADMAP

XPRIZE®

IN PARTNERSHIP WITH

Sergey Young

LEADERSHIP

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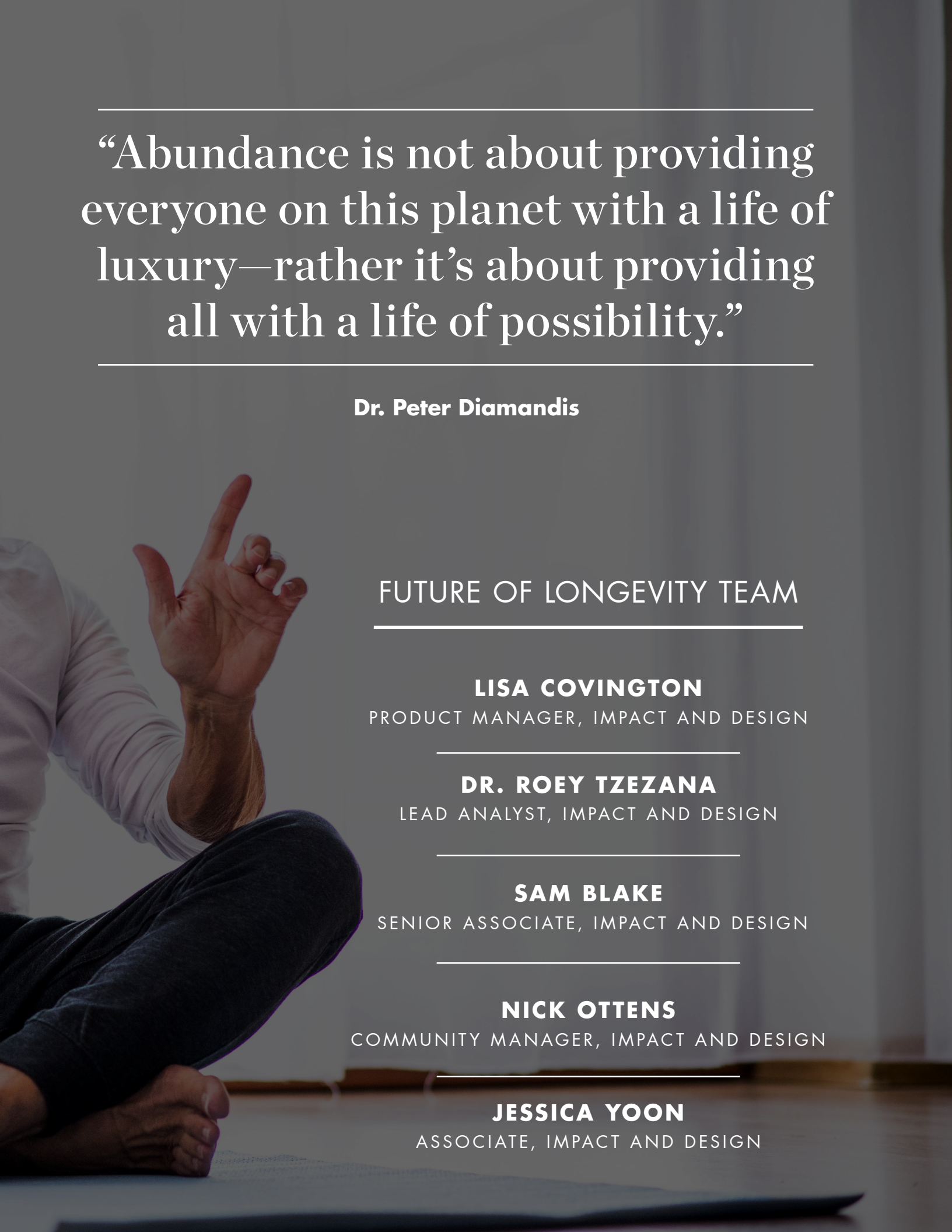

"Abundance is not about providing everyone on this planet with a life of luxury—rather it's about providing all with a life of possibility."

Dr. Peter Diamandis

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Foreword by Aubrey de Grey

THE SINGLE MOST important determinant of an individual's quality of life is their health. When you're sick, nothing in life is as fulfilling until you get well again. And there is, of course, a point in the lives of at least 90% of those in the industrialised world (and, by now, at least half of the developing world, too) at which one's health departs never to return, because the conditions one has acquired are among the chronic, inexorably progressive aspects of aging.

Since the dawn of civilisation, the above truth has hung over us like the blackest of clouds. So thoroughly has it dominated our view of life that we have been forced to find psychological tricks to put it out of our minds, rather than have our existence contaminated by preoccupation with it. The Epic of Gilgamesh, the Myth of Tithonus—even the ancients came up with ways to convince themselves that aging and the death that it inescapably presages is some sort of blessing in disguise. Some would say that the whole of religion is in this category. Certainly this is true of the blinding irrationality exhibited by so many of us regarding the desirability of the main side-effect that the medical extension of youth would have, namely the extension of lifespan.

The situation has been made worse, if anything, by the succession of claims to having discovered the "fountain of youth"—the elixir that can hold back the decline of aging and maintain youth indefinitely, or at least dramatically. The reason these claims are a problem, of course, is that none of them has actually been valid. We still exhibit age-related decline, just as our forefathers did, and at only slightly greater ages—and the slight rise that we have seen has, in most experts' view, been largely down to greater prosperity and consequently better nutrition, especially in early life.

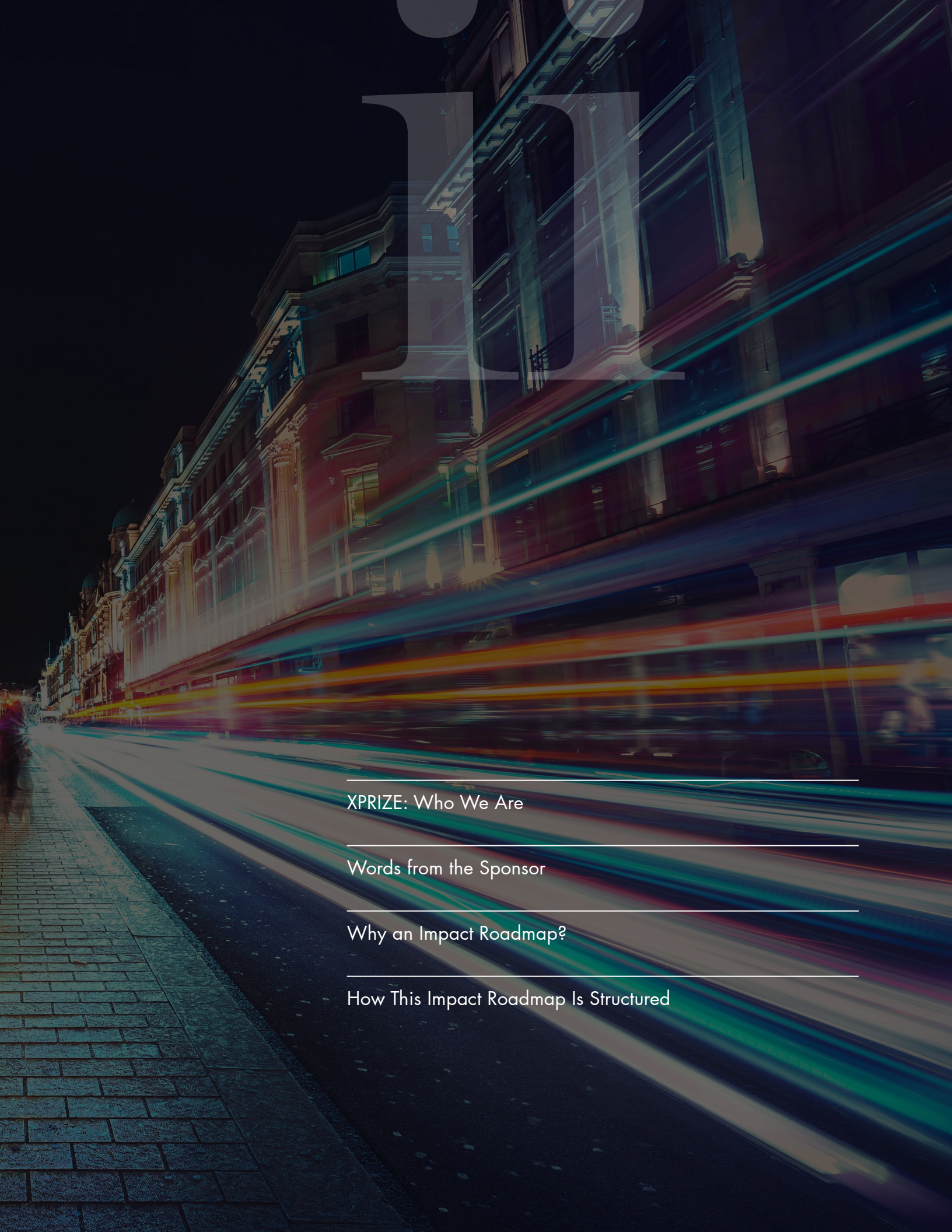
Thus it is that, today, in spite of all the breathtaking advances that have been made in medicine over the past century or two, there remains an obstinately unshakeable conviction in most people's minds that aging is in some profound, albeit undefinable, way off limits to medicine, such that future attempts to extend youth will be as quixotic as past ones. Experts who know, and protest, that this conviction has no biological basis whatever are often treated more as entertainers than as researchers. At best, most people will believe it when they see it.

Thus, aging is a perfect topic for an XPRIZE. Progress on the most daunting problems facing humanity relies on the efforts of those who are courageous—unreasonable, as George Bernard Shaw put it ("All progress depends on the unreasonable man")—enough to withstand this ridicule and to devise ways to transcend our limitations. And it can forcefully be argued that no problem fits this description better than aging. We're seeing medicines achieve more against aspects of aging than ever before, but we still need to speed it up a lot—and XPRIZE is set to play a huge part in doing just that.

AUBREY DE GREY

ii.

PREFACE: UNDERSTANDING AGING



Who We Are

AT XPRIZE, our mission is to inspire and empower a global community of problem-solvers to positively impact our world. We believe solutions to the world's problems can come from anyone, anywhere.

Our role is to define the problems, set the targets, and crowdsource solutions through global competitions to incentivize the development of technological breakthroughs that accelerate humanity toward a better future. We provide the opportunity and the platform for people to take risks that ultimately lead to solutions that seemed out of reach or impossible. Instead of simply celebrating great ideas, we reward innovators who follow through on their vision and create tangible solutions that are validated through extensive testing and judging.

The first-ever XPRIZE competition, the $10 Million Ansari XPRIZE for sub-orbital spaceflight, captured the world's imagination and catalyzed a multi-billion-dollar commercial space industry, representing a massively leveraged initial philanthropic investment. Since then, we have launched seventeen competitions in the areas of Energy, the Environment, Civil Society, Human Health & Longevity, Learning, Exploration, and Mobility.

Words from the Sponsor

HELPING PEOPLE TO live longer, healthier and happier lives has been my lifelong mission. As an investor, I am able to use the deep insights gained into the longevity industry, to extend human lifespan and overcome the negative effects of aging on a worldwide level.

We are on the brink of a Longevity Revolution: a world where everybody can live a long, healthy, high-quality life; where previously incurable diseases can finally be treated; and where the aging process itself can be slowed, stopped, or even reversed. This is the world we want for ourselves, our children, and for everybody else. We are about to step into this new paradigm, and I hope this Future of Longevity Impact Roadmap will help to illuminate the path to achieving it.

-SERGEY YOUNG

Why an Impact Roadmap?

AN IMPACT ROADMAP is an analytical tool for understanding persistent problems and barriers that make up Grand challenges in various domains, as well as the actions that key stakeholders can take to overcome them and achieve a preferred future state. Grand Challenges comprise a combination of complex and overlapping social, technological, economic, environmental and policy issues. An Impact Roadmap will identify these challenges and highlight the most effective actions to address them and accelerate progress toward a more positive future.

XPRIZE is using Impact Roadmaps to help identify potential XPRIZE competitions and other actions that can accelerate a bridge to abundance for all, in domains including shelter and infrastructure; energy and resources; planet and environment; health and wellness; learning and human potential; civil society; and space and new frontiers.

Emerging, exponential technologies and other innovations in policy and financing have the potential to address grand challenges in these areas, but they require new action by key stakeholders and innovators from around the globe. By promoting the use of exponential technologies in disruptive new ways, XPRIZE is aiming to help create a better world—today.

How This Impact Roadmap Is Structured

THIS FUTURE OF Longevity Impact Roadmap is split into several interlinked sections. We begin with a **PREFERRED FUTURE STATEMENT** for longevity. This statement establishes an aspirational vision to guide our analysis. By beginning with this vision in mind, we can systematically work backwards from it to understand what is needed to achieve such a future.

We then examine the **OBSTACLES** to achieving such a future, and explore the existing and emerging **REMEDIES** for these obstacles. Through this analysis we arrive at five **GRAND CHALLENGES** of longevity. We then identify several **BREAKTHROUGHS** that, if achieved, can overcome the grand challenges, and we conclude with **SCENARIOS** to bring to life several possible futures of longevity.

WANT TO JUMP STRAIGHT TO THE BREAKTHROUGH SOLUTIONS? TURN TO PAGE 200 TO EXPLORE THE GAME-CHANGERS WE'VE IDENTIFIED THAT COULD SIGNIFICANTLY ACCELERATE THE FIELD OF LONGEVITY.

PREFERRED FUTURE STATEMENT

IN OUR PREFERRED FUTURE:

- THE BIOLOGICAL AGING PROCESS WILL BE DRAMATICALLY DELAYED THROUGH WIDELY AVAILABLE INTERVENTIONS THAT EXTEND HUMAN LIFESPAN AND HEALTHSPAN;
- AGING-RELATED ILLNESS WILL BE EXTREMELY RARE, AND PHYSICAL AND COGNITIVE DETERIORATION DUE TO AGING WILL BE GREATLY REDUCED; AND
- HUMANITY WILL EMBRACE THE ABILITY TO REMAIN HEALTHY AND YOUTHFUL FOR A MUCH LONGER TIME THROUGHOUT THEIR PHYSICALLY, MENTALLY, AND EMOTIONALLY HEALTHY LIVES.

THIS STATEMENT IS OUR SOCIETAL ASPIRATION. IT SERVES AS A LODESTAR FOR OUR RESEARCH. OUR GOAL IS TO IDENTIFY WHAT IS KEEPING US FROM ACHIEVING IT, AND WHAT MUST BE DONE TO ACCELERATE ITS ARRIVAL.

01.

EXECUTIVE SUMMARY

Introduction

AN IMPACT ROADMAP is a tool used by XPRIZE to systematically analyze a given domain. One key reason for doing so is to guide the strategic design of future XPRIZE competitions.

This Future of Longevity Impact Roadmap examines how our collective understanding of human life is changing, and what that means for our health and wellness. The goal of this report is to describe the current state of the field of longevity, identify where it may go in the future, and highlight key steps for ensuring that the future of longevity is the best one for humanity at large.

Our research has been supported by the ongoing input of dozens of multidisciplinary experts from across the globe. With their help, we have explored the current state and potential futures of longevity to better understand the most critical aspects of the domain. We have also sought to inspire new thinking and action that will catalyze innovation towards a **preferred future** of increased lifespan and healthspan for all.

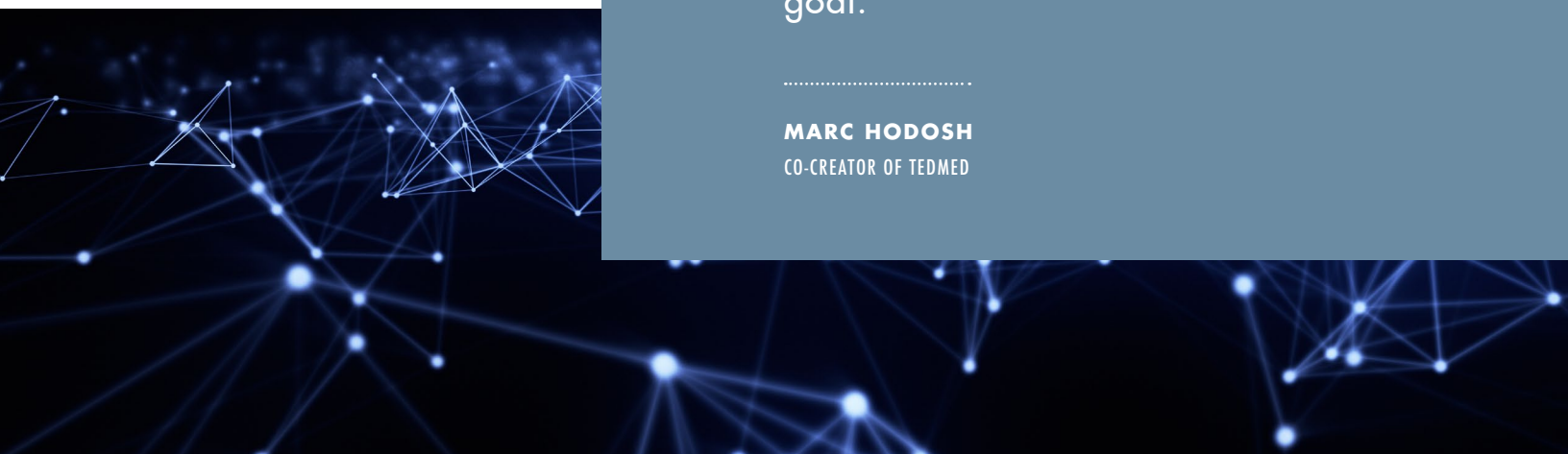
In this report, we identify five **grand challenges** of longevity, which together represent the most pressing issues holding back the field. To arrive at these grand challenges, we analyzed 19 **obstacles** to achieving a preferred future state of longevity, and 28 **remedies**, which comprise some of the most relevant countermeasures taken today to deal with each obstacle. These existing and emerging remedies, however, generally fall short of success. We examine the reasons for their shortcomings in the gaps sub-section of each grand challenge.

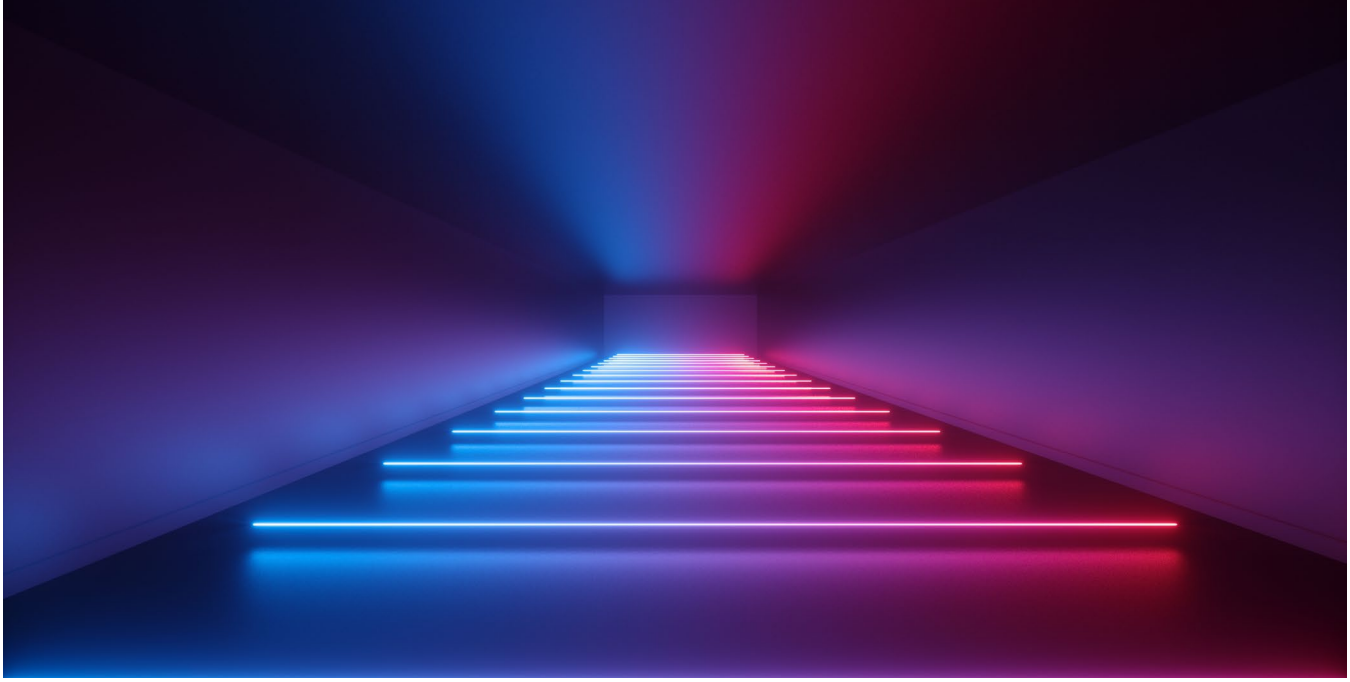
Through analyzing the grand challenges and gaps, we have developed several **breakthrough solutions** that could help to overcome them. We administered an expert survey to assess the audacity and expected impact of each breakthrough, as well as the expected timeline for their fulfillment.

We conclude the report by exploring four potential scenarios for the future of longevity in the year 2040. In each future scenario, a different variety of grand challenges has been solved via the successful development and implementation of various breakthroughs. Through these scenarios, we bring to life the different ways in which the future could unfold.

"Curing all age-related diseases and adding healthy years to our lives is perhaps the most significant and greatest challenge of humanity. XPRIZE is well positioned to inspire new research in aging, by educating and energizing society towards supporting this important goal."

MARC HODOSH
CO-CREATOR OF TEDMED





Preferred Future of Longevity

THIS STATEMENT IS our societal aspiration. It serves as a lodestar for our research. Our goal is to identify what is keeping us from achieving it, and what must be done to accelerate its arrival.

In our preferred future:

» The biological aging process will be dramatically delayed through widely available interventions that extend human lifespan and healthspan;

» Aging-related illness will be extremely rare, and physical and cognitive deterioration due to aging will be greatly reduced; and

» Humanity will embrace the ability to remain healthy and youthful for a much longer time throughout their physically, mentally, and emotionally healthy lives.

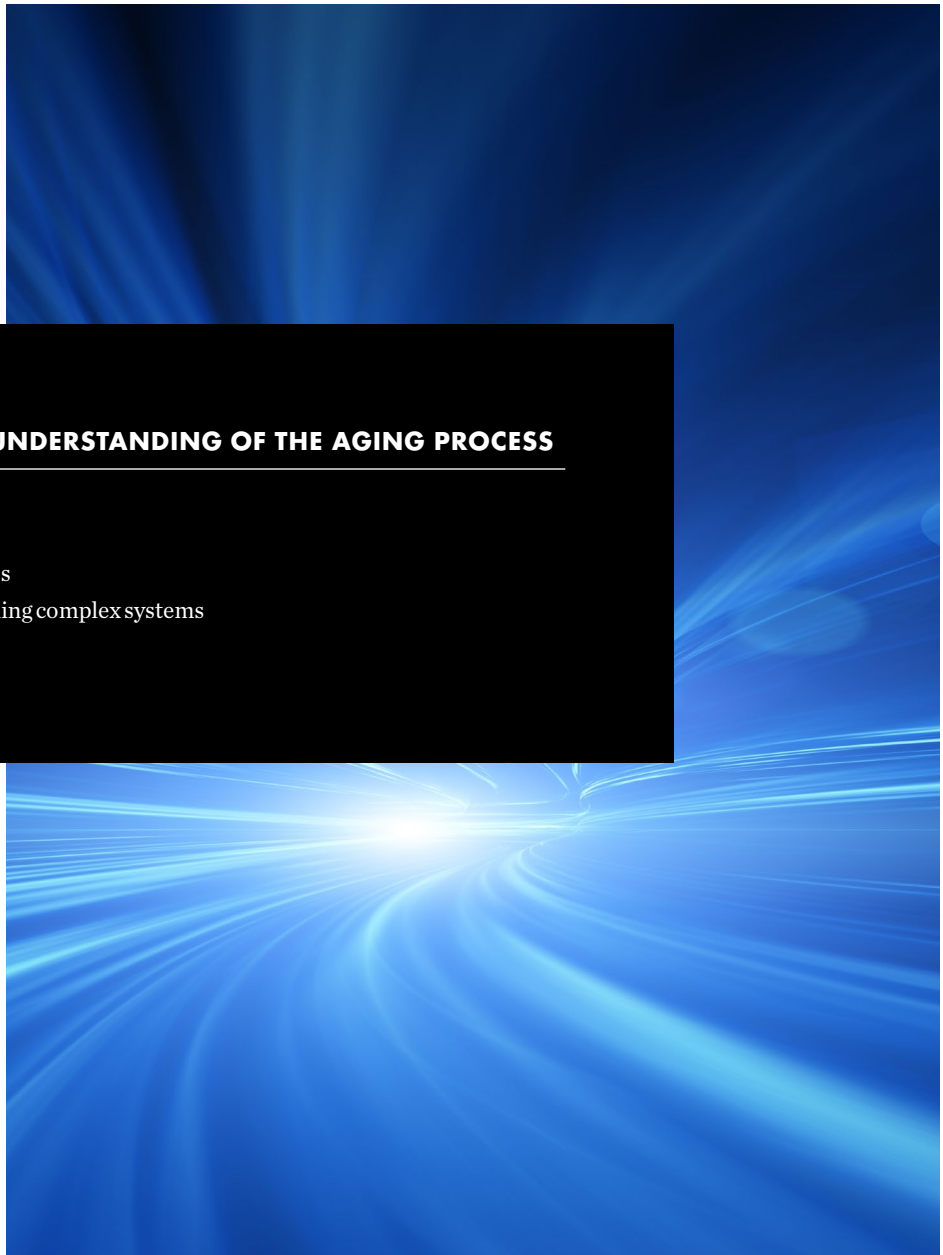
Grand Challenges and Gaps

THE FOLLOWING GRAND challenges and their associated gaps are derived from our analysis of the obstacles to achieving a preferred future state of longevity, the current remedies to address those obstacles, and the reasons these remedies are falling short.

GRAND CHALLENGE #1

Advancing Scientific Understanding of the Aging Process

ALTHOUGH THE DISTILLATION of the formidably complex aging process into more manageable molecular and cellular changes has made creating longevity treatments much more viable, the aging process continues to mystify. Uncertainty remains, for example, about the cause and effect dynamics among the various changes that accompany aging. Such knowledge gaps slow progress in the field. An improved understanding of how the different mechanisms and indicators of aging relate to each other would empower researchers and innovators to make more informed and effective decisions about how to intervene in the human aging process.



GAPS FOR ADVANCING SCIENTIFIC UNDERSTANDING OF THE AGING PROCESS

- No accurate models to experiment on
- Lack of consensus on biomarkers
- Imaging tools are lacking in capabilities
- Limited human capacity for understanding complex systems
- Lack of funding

GAPS FOR IMPROVING TREATMENT TOOLS

- Technological limitations
- Risky technology
- Ideological objections
- Unclear ethics

GRAND CHALLENGE #2

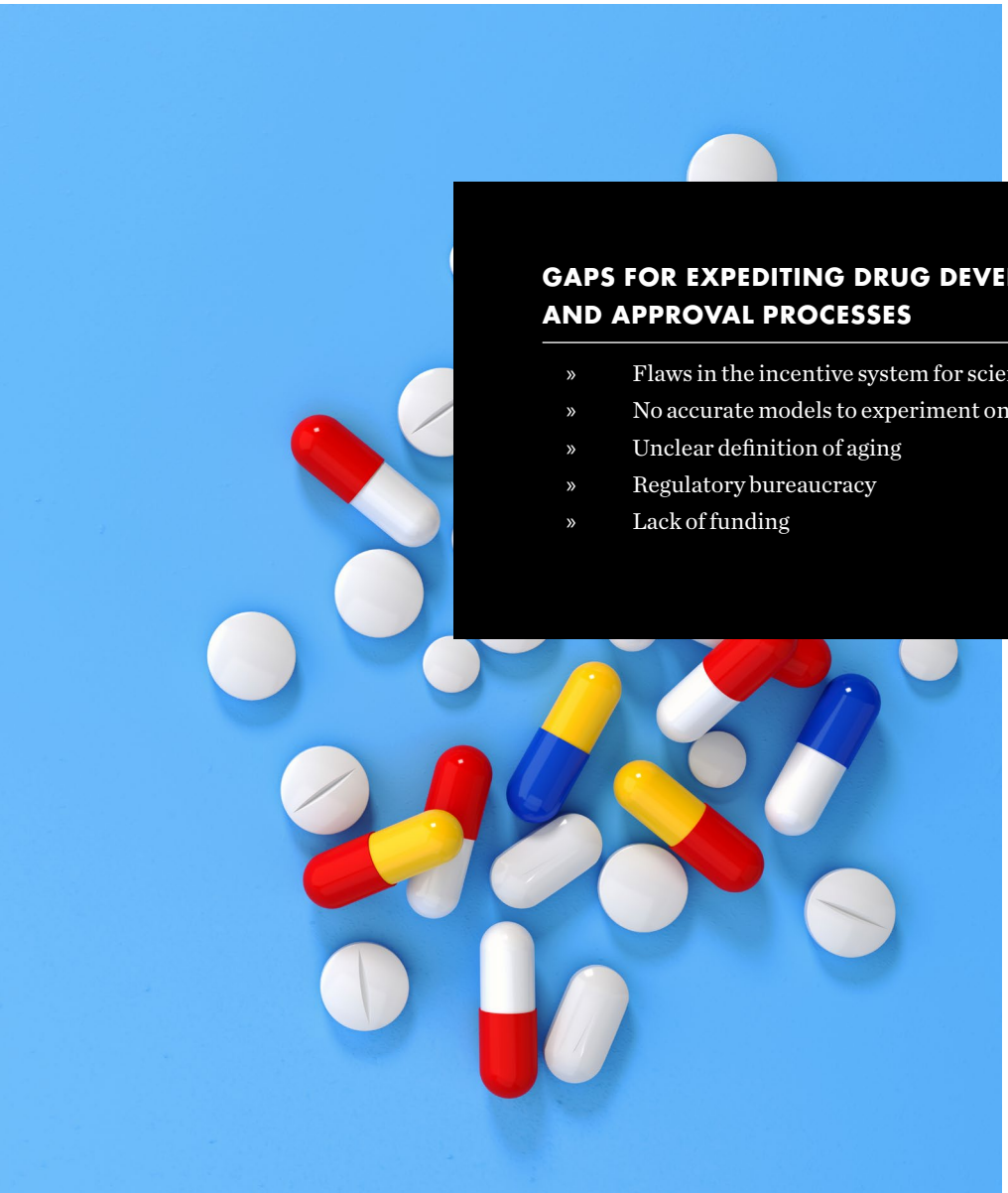
Improving Treatment Tools

THERE IS AN urgent need for better tools to counter and treat the aging process. Existing tools either lack the necessary precision or remain to be proven effective in large sample sizes. Numerous tools are emerging—including genetic and epigenetic engineering, and stem cell therapy—but each treatment comes with limitations and risks. As a result, these tools currently struggle to achieve mainstream uptake.

GRAND CHALLENGE #3

Expediting Drug Development and Approval Processes

THE HEAVY BURDEN of earning regulatory approval is a significant hurdle to the development and dissemination of treatments, both for the consequences and especially for the causes of aging. This limits innovation to a select few players capable of bearing such investments. Even among those who can do so, the process is fraught with failures. At most, only 13.8% of all drug candidates that enter phase I of clinical trials end up being approved by the FDA. The entire process of clinical trials and FDA approval usually takes between six to 10 years. The fourth, post-market, phase can take up to 10 additional years. Other drug approval authorities worldwide impose similar timelines.



GAPS FOR EXPEDITING DRUG DEVELOPMENT AND APPROVAL PROCESSES

- Flaws in the incentive system for scientific activities
- No accurate models to experiment on
- Unclear definition of aging
- Regulatory bureaucracy
- Lack of funding

GRAND CHALLENGE #4

Raising Public Awareness and Improving Public Perception

THE GENERAL PUBLIC is largely unaware of longevity science, and is oblivious to the potential it holds for improved quality of life. Articles that expose laypeople to news about developments in longevity science are often written in a sensationalistic manner that either emphasizes the negative potential impact of treatments or dismisses the idea altogether. The result of this situation is that there is a lack of public and political will toward funding longevity studies. Limited public pressure also means that some highly-needed legal decisions about longevity studies are not being fulfilled: aging, for example, has yet to be classified as a disease. Thus, even pharmaceutical companies hesitate to develop drugs in this sector, as it is not clear whether there will be a regulatory path for them. It is likely that without greater public acceptance and pressure, many governing bodies will overlook or even disregard developments in the field.

GAPS FOR RAISING PUBLIC AWARENESS AND IMPROVING PUBLIC PERCEPTION

- Misinformation
- Lack of information
- Ideological objections
- Lack of funding
- Negative perception of life extension advocates

GRAND CHALLENGE #5

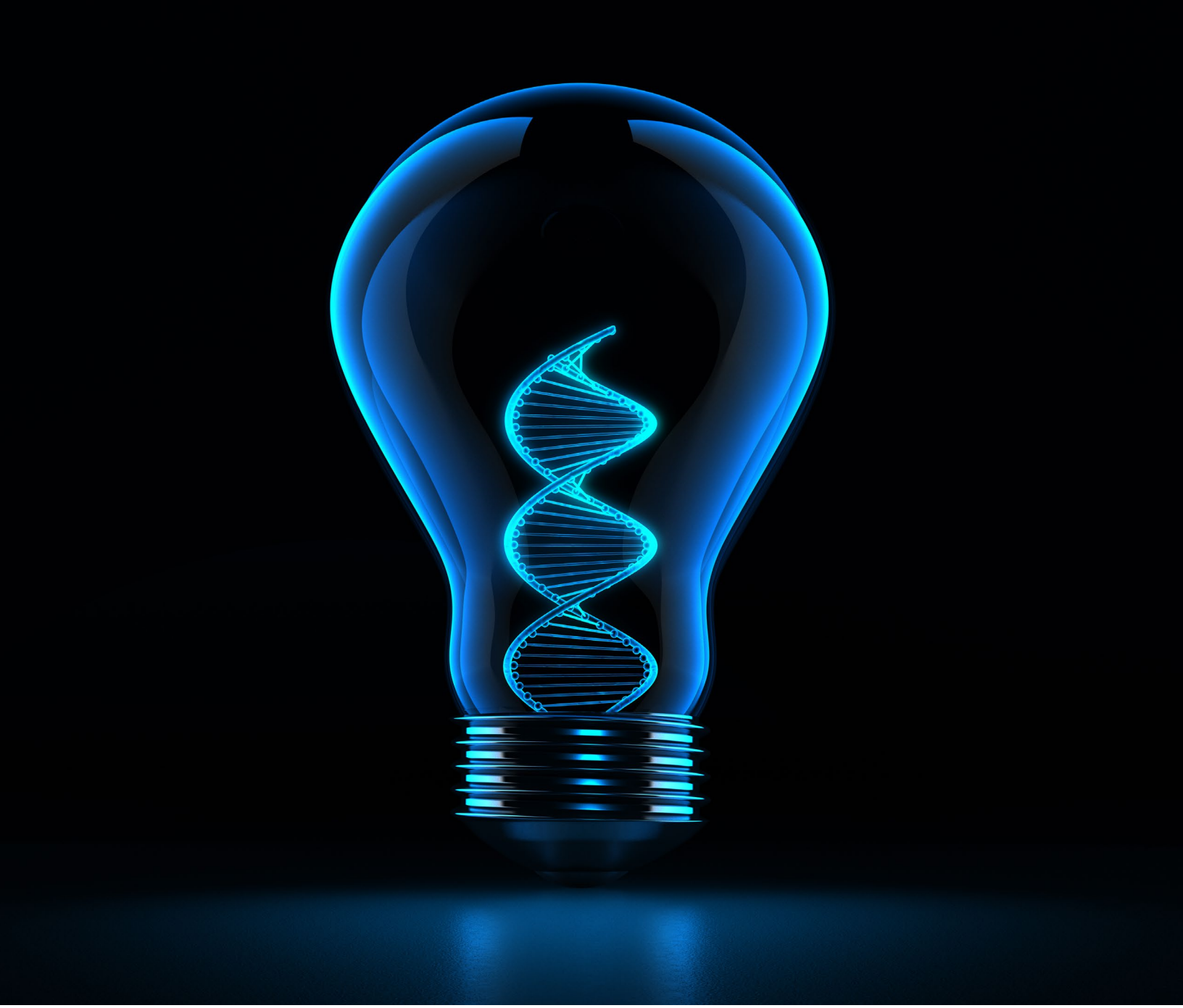
Ensuring Accessibility of Treatments

THERE IS A general consensus that longevity treatments should eventually be accessible to all. Medical treatments, however, are typically expensive when they're first released to the market, often due to high development costs and patent protections. High-priced longevity treatments may mean that many people will not be able to afford them, which could breed greater social and economic disparities in virtually every part of the world.

Another challenge in ensuring the accessibility of treatments is that most medical doctors receive almost no medical training in aging and biogerontology, and so do not realize that tackling aging is the best way to tackle many aging-related diseases. Medical doctors are often unaware of the new breakthroughs in aging research, and thus look down upon or discard notions that aging can be addressed. Even when they're aware of the longevity potential of some drugs, they may find it difficult to prescribe them to patients who are not yet diagnosed with any sort of sickness, but are only experiencing "natural" aging.

GAPS FOR ENSURING ACCESSIBILITY OF TREATMENTS

- Dealing with high treatment costs
- Methods of distribution
- Integration into healthcare systems
- Laws



Breakthroughs

THE FOLLOWING BREAKTHROUGHS represent a collection of possible solutions for overcoming the identified grand challenges of longevity. Forecast and assessment data were collected via an expert survey.

BREAKTHROUGH #1

Aging, Shared: A shared database to collect real-time aging data

- **EXPECTED YEAR FOR PROOF OF CONCEPT:** 2022
- **EXPECTED YEAR FOR MASS-SCALING:** 2030
- **IMPACT (1-10):** 6
- **AUDACITY (1-10):** 3

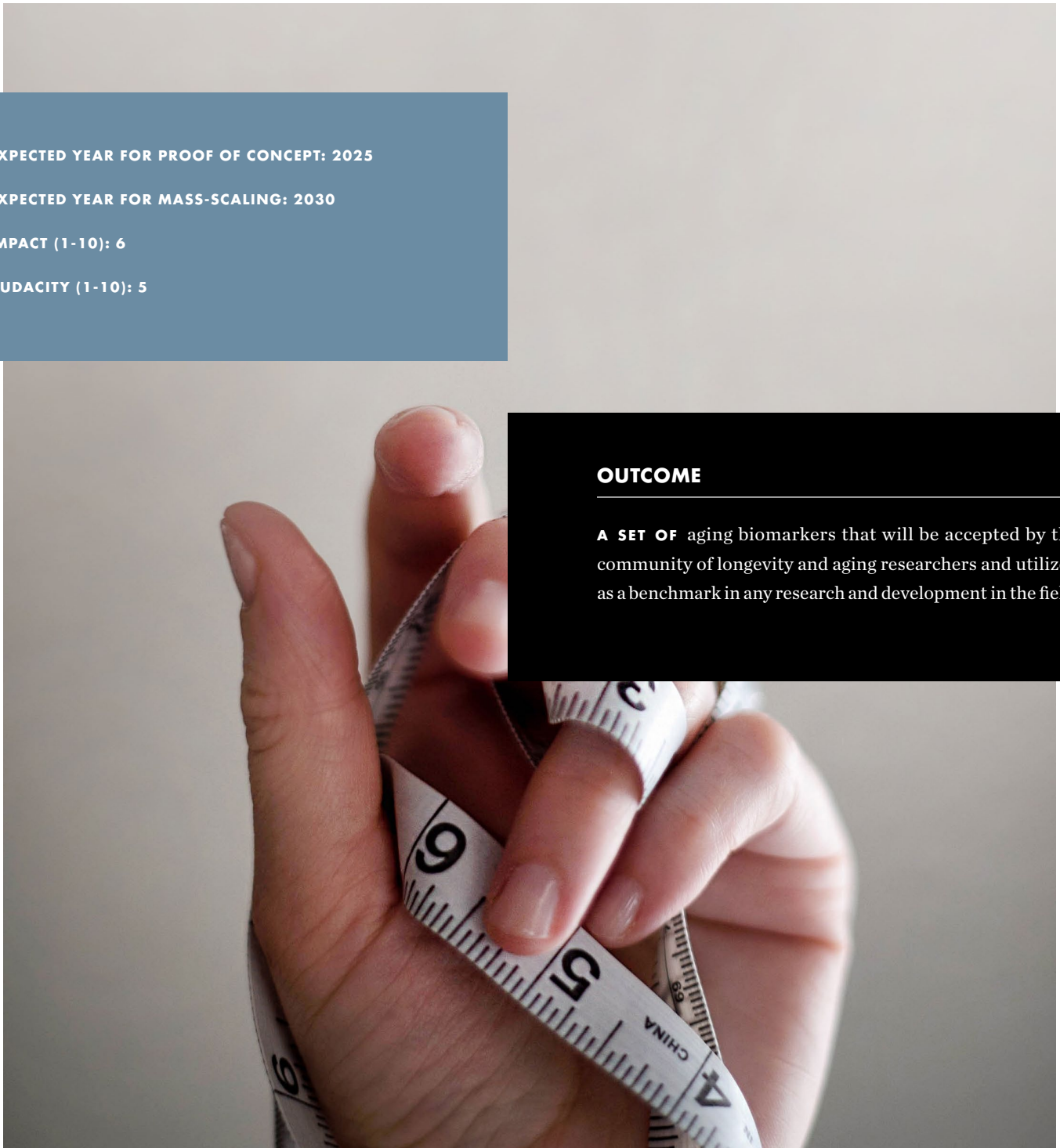
OUTCOME

A LEDGER IN which real-time data will be collected from individuals, to track their vital signs and lifestyle choices and activities.

BREAKTHROUGH #2

Aging, Quantified: A set of widely agreed-upon biomarkers for measuring biological age

- EXPECTED YEAR FOR PROOF OF CONCEPT: 2025
- EXPECTED YEAR FOR MASS-SCALING: 2030
- IMPACT (1-10): 6
- AUDACITY (1-10): 5

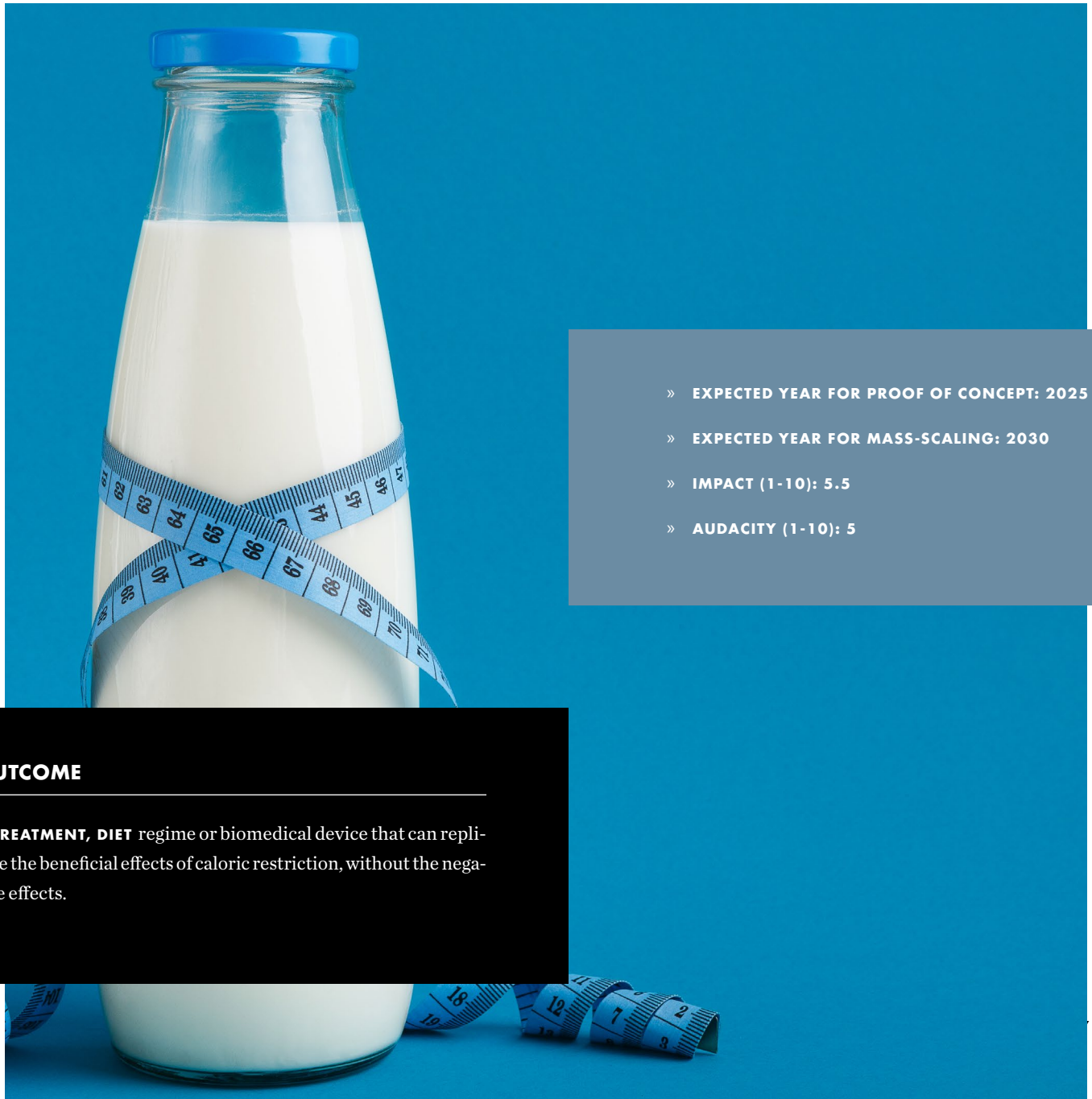


OUTCOME

A SET OF aging biomarkers that will be accepted by the community of longevity and aging researchers and utilized as a benchmark in any research and development in the field.

BREAKTHROUGH #3

Caloric Restriction for All: Replicating the beneficial effects of caloric restriction, without the negative effects



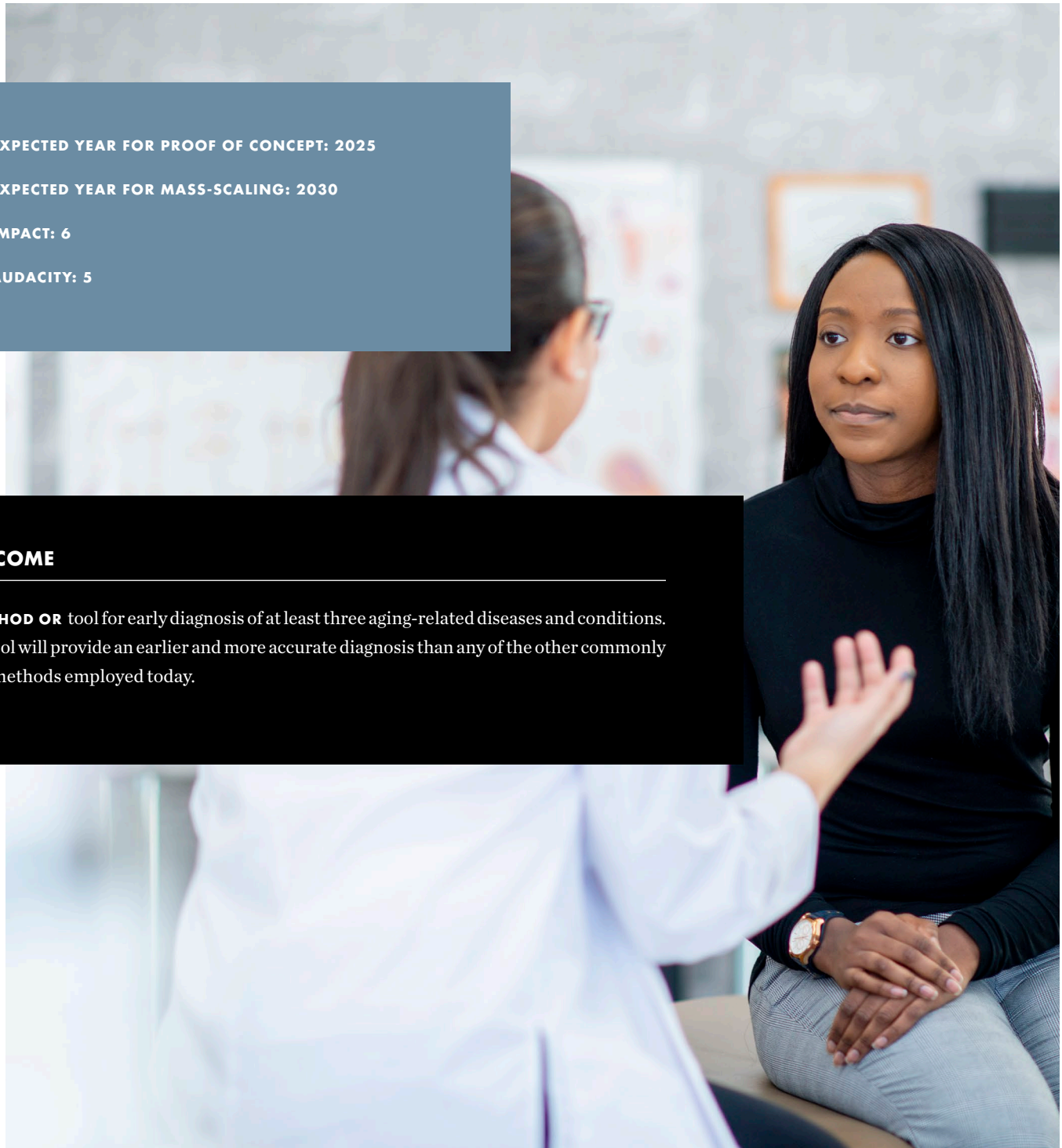
- EXPECTED YEAR FOR PROOF OF CONCEPT: 2025
- EXPECTED YEAR FOR MASS-SCALING: 2030
- IMPACT (1-10): 5.5
- AUDACITY (1-10): 5

OUTCOME

A TREATMENT, DIET regime or biomedical device that can replicate the beneficial effects of caloric restriction, without the negative effects.

BREAKTHROUGH #4

Preparing for Aging: Early diagnosis of aging-related diseases and conditions



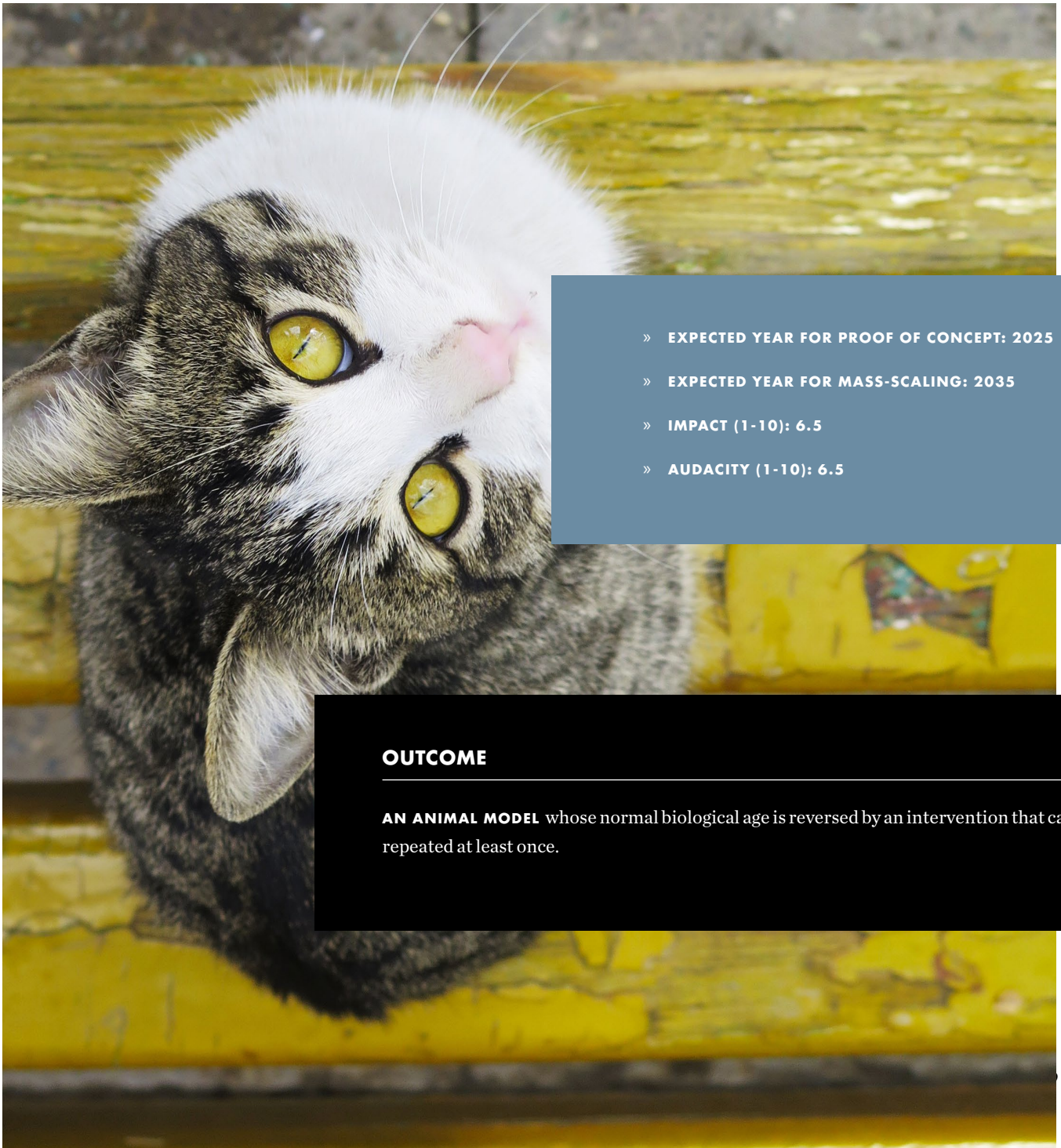
- EXPECTED YEAR FOR PROOF OF CONCEPT: 2025
- EXPECTED YEAR FOR MASS-SCALING: 2030
- IMPACT: 6
- AUDACITY: 5

OUTCOME

A METHOD OR tool for early diagnosis of at least three aging-related diseases and conditions. The tool will provide an earlier and more accurate diagnosis than any of the other commonly used methods employed today.

BREAKTHROUGH #5

The Age-Reversed Animal: Demonstrating age-reversal in an animal model



- EXPECTED YEAR FOR PROOF OF CONCEPT: 2025
- EXPECTED YEAR FOR MASS-SCALING: 2035
- IMPACT (1-10): 6.5
- AUDACITY (1-10): 6.5

OUTCOME

AN ANIMAL MODEL whose normal biological age is reversed by an intervention that can be repeated at least once.

BREAKTHROUGH #6

Aging, Delayed: Postponing the emergence of at least three aging-related diseases or conditions with the same treatment

- EXPECTED YEAR FOR PROOF OF CONCEPT: 2030
- EXPECTED YEAR FOR MASS-SCALING: 2035
- IMPACT (1-10): 7
- AUDACITY (1-10): 6

OUTCOME

POSTPONING THE EMERGENCE of at least three aging-related diseases or conditions with the same treatment. This will demonstrate that the emergence of aging-related diseases and conditions can be postponed and delayed, not one disease at a time, but instead by targeting more upstream factors related to aging.

BREAKTHROUGH #7

Homeostasis Restored: Constant analysis of the body's capacity to uptake nutrients and the bioavailability of critical biomolecules

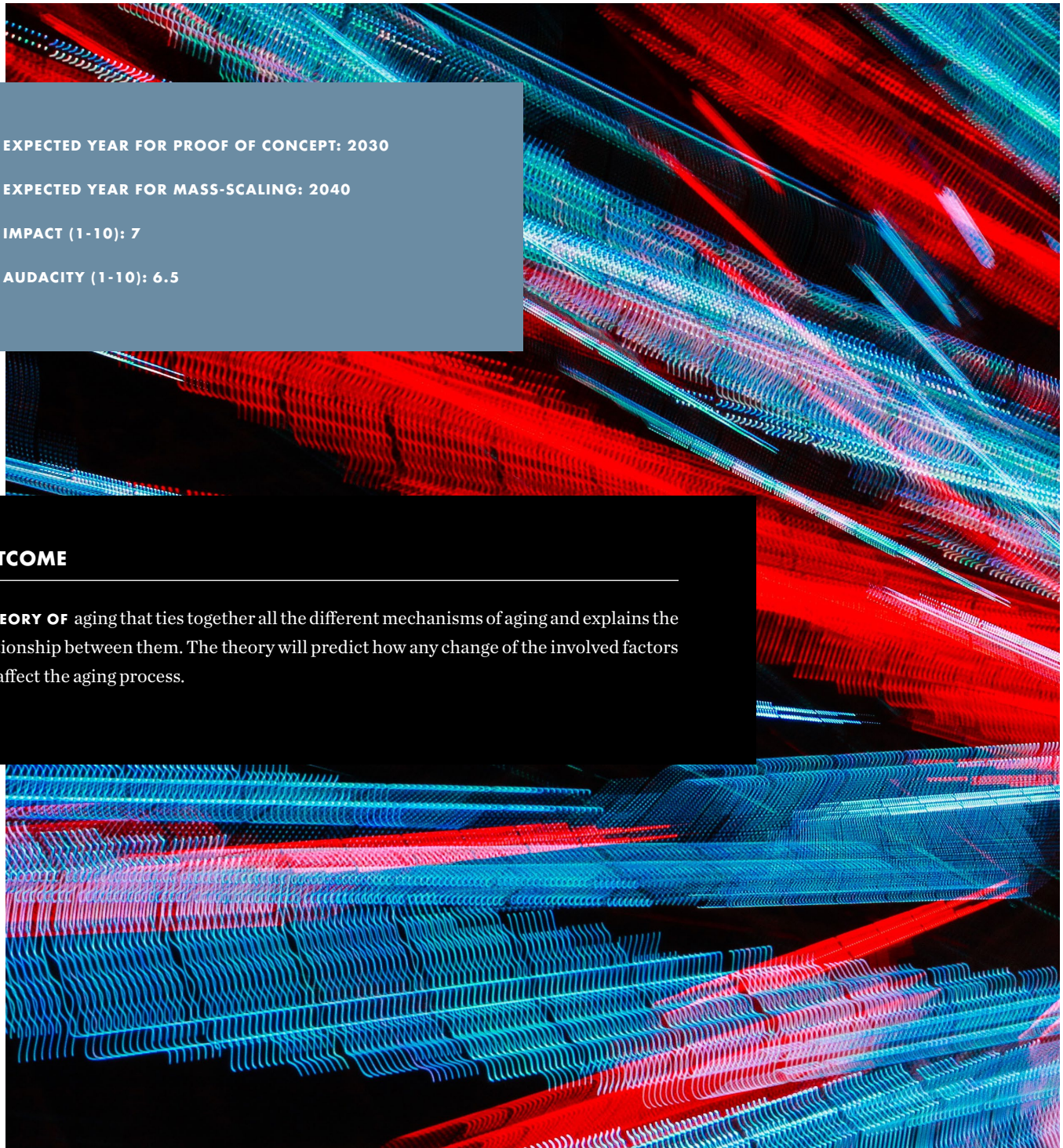
- EXPECTED YEAR FOR PROOF OF CONCEPT: 2030
- EXPECTED YEAR FOR MASS-SCALING: 2035
- IMPACT (1-10): 6
- AUDACITY (1-10): 5.5

OUTCOME

A SOLUTION THAT will analyze in real time people's capacity to uptake nutrients, as well as the bioavailability of critical biomolecules in their body, and provide actionable advice on how to restore youthful levels.

BREAKTHROUGH #8

Aging, Understood: A Robust Theory of Aging



- EXPECTED YEAR FOR PROOF OF CONCEPT: 2030
- EXPECTED YEAR FOR MASS-SCALING: 2040
- IMPACT (1-10): 7
- AUDACITY (1-10): 6.5

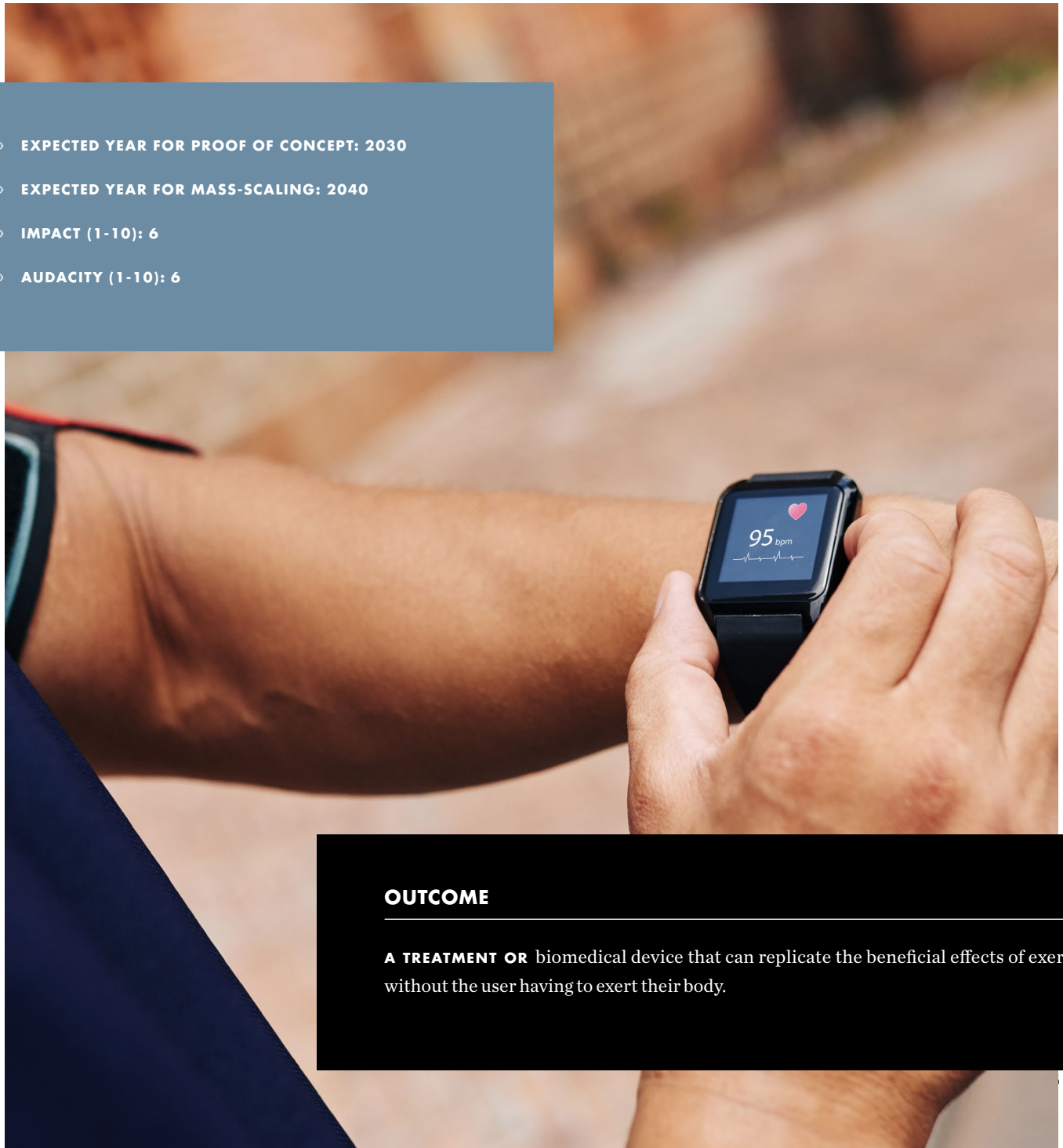
OUTCOME

A THEORY OF aging that ties together all the different mechanisms of aging and explains the relationship between them. The theory will predict how any change of the involved factors will affect the aging process.

BREAKTHROUGH #9

Exercise Made Easy: Replicating the beneficial effects of exercise, without the need to exert the body

- EXPECTED YEAR FOR PROOF OF CONCEPT: 2030
- EXPECTED YEAR FOR MASS-SCALING: 2040
- IMPACT (1-10): 6
- AUDACITY (1-10): 6



OUTCOME

A TREATMENT OR biomedical device that can replicate the beneficial effects of exercise, without the user having to exert their body.

BREAKTHROUGH #10

Aging, Arrested: Stopping the body's aging process for at least one year

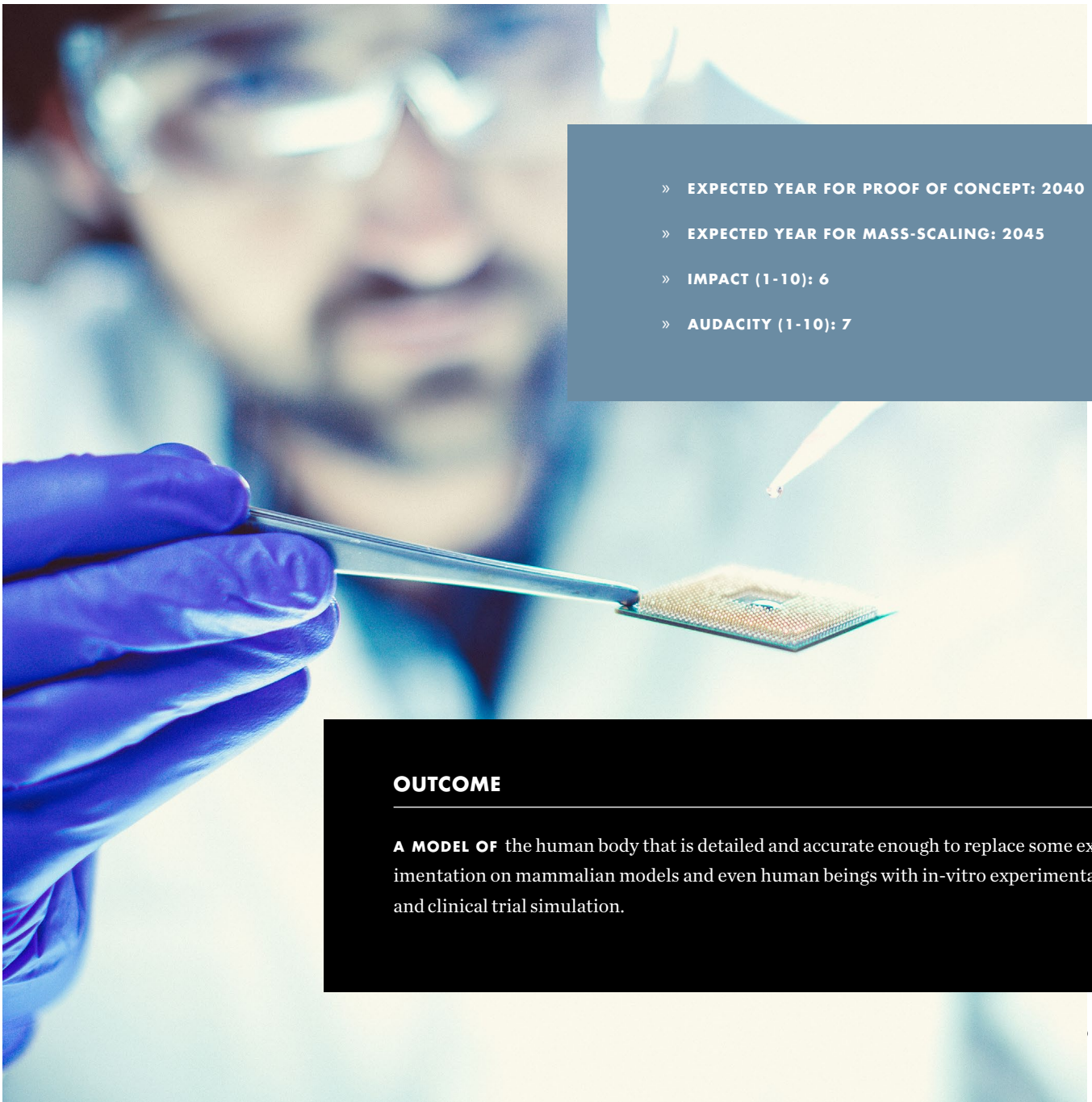
- EXPECTED YEAR FOR PROOF OF CONCEPT: 2035
- EXPECTED YEAR FOR MASS-SCALING: 2048
- IMPACT (1-10): 6.5
- AUDACITY (1-10): 7

OUTCOME

A TREATMENT FOR completely stopping the body's aging process for at least one year. The treatment will likely be demonstrated on mammals first, and will later be translated to human beings.

BREAKTHROUGH #11

In Silico Aging: Creating a detailed and accurate model of the human body, for high-capacity in-vitro experimentation



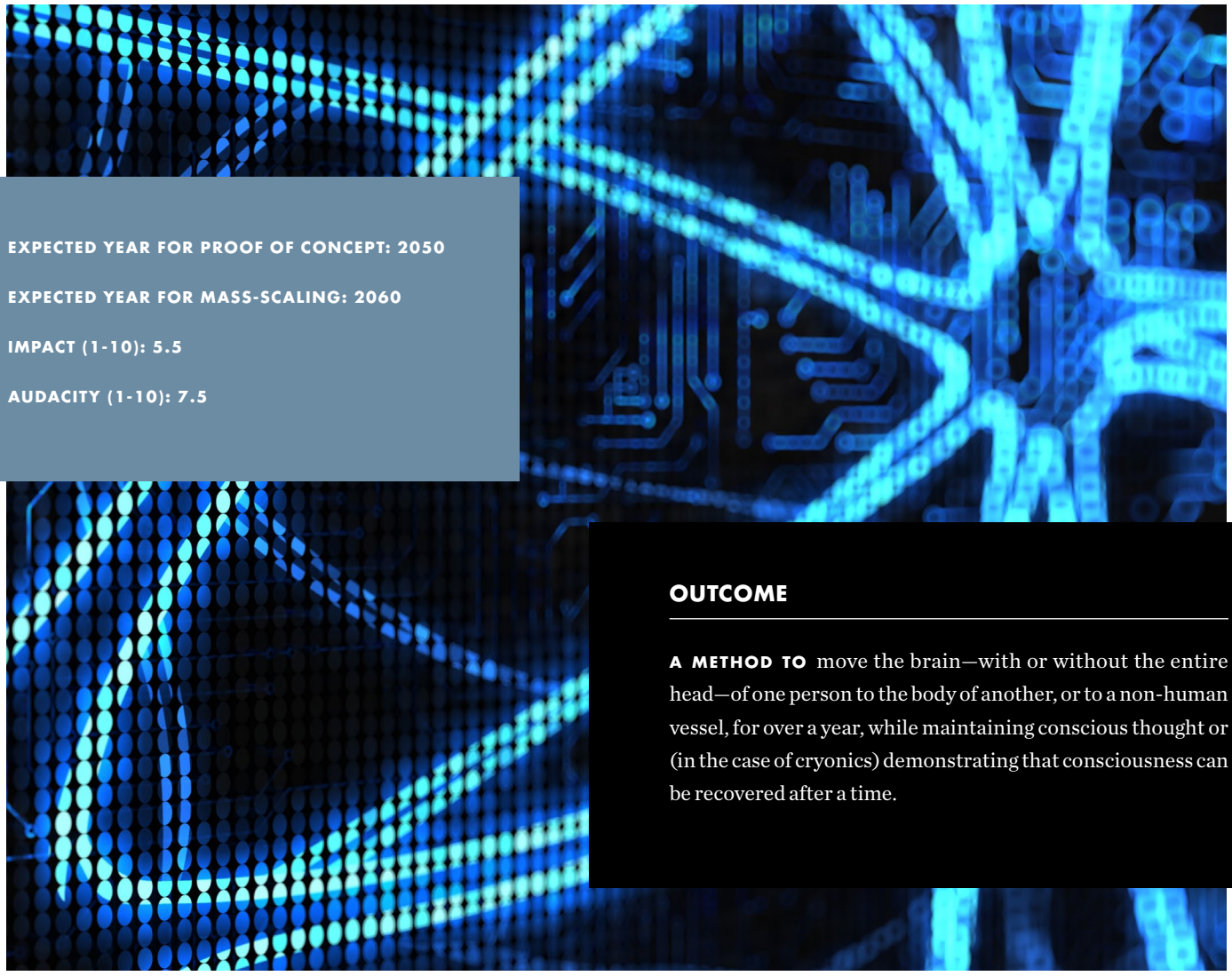
- EXPECTED YEAR FOR PROOF OF CONCEPT: 2040
- EXPECTED YEAR FOR MASS-SCALING: 2045
- IMPACT (1-10): 6
- AUDACITY (1-10): 7

OUTCOME

A MODEL OF the human body that is detailed and accurate enough to replace some experimentation on mammalian models and even human beings with in-vitro experimentation and clinical trial simulation.

BREAKTHROUGH #12

Aging, Circumvented: A way to safely detach the brain from the aging body



- EXPECTED YEAR FOR PROOF OF CONCEPT: 2050
- EXPECTED YEAR FOR MASS-SCALING: 2060
- IMPACT (1-10): 5.5
- AUDACITY (1-10): 7.5

OUTCOME

A METHOD TO move the brain—with or without the entire head—of one person to the body of another, or to a non-human vessel, for over a year, while maintaining conscious thought or (in the case of cryonics) demonstrating that consciousness can be recovered after a time.

EXPERT ASSESSMENT OF BREAKTHROUGHS

Figure 1.1 shows the expected dates of fulfillment for each breakthrough solution, while Figure 1.2 depicts each breakthrough's impact versus audacity ranking. Both figures are based on data collected via a survey of 59 expert respondents.

FIGURE 1.1: EXPECTED DATES OF BREAKTHROUGHS

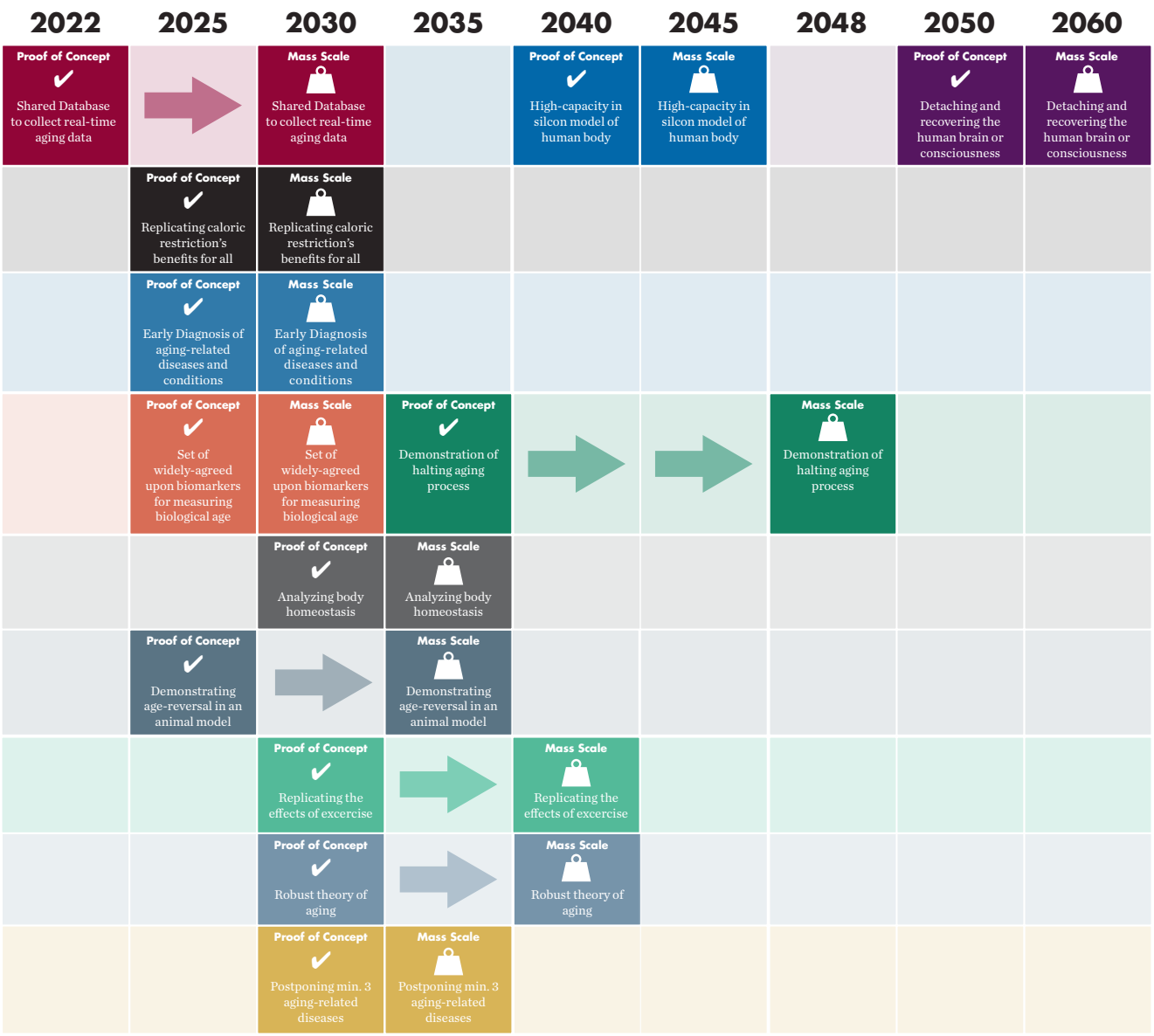
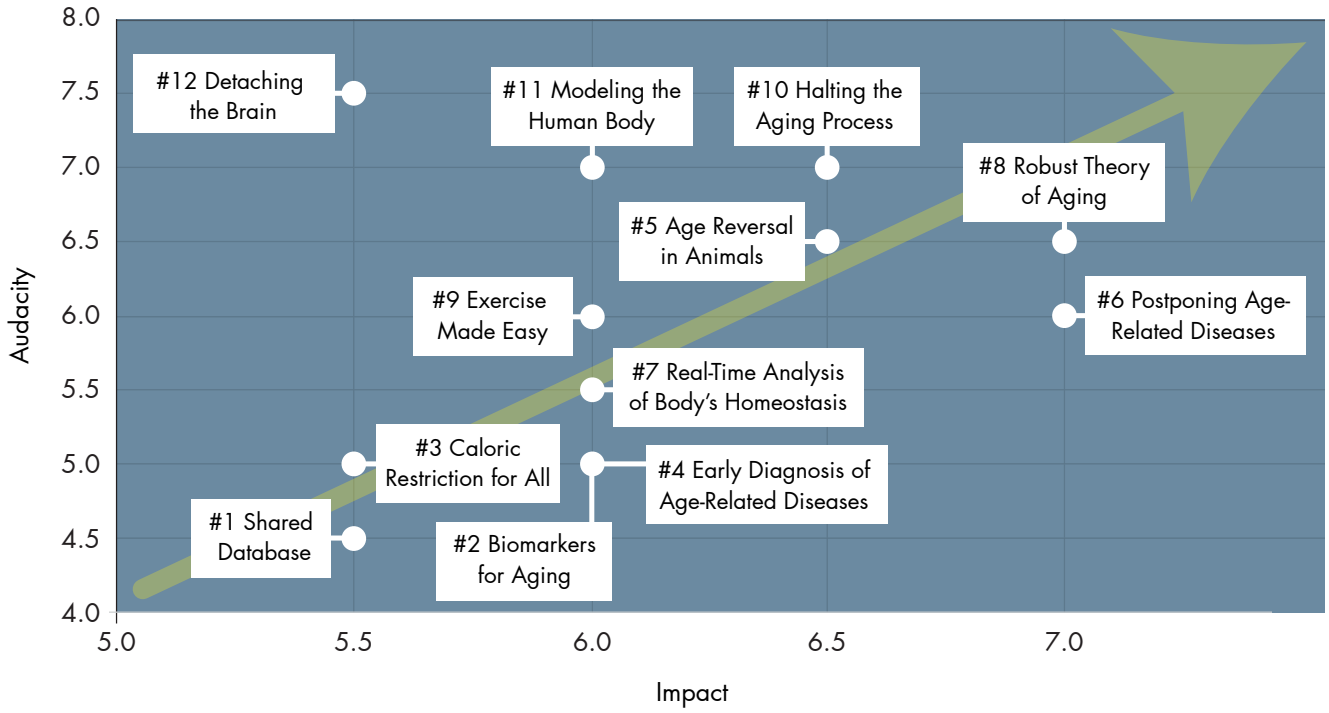


FIGURE 1.2: BREAKTHROUGH IMPACT VS. AUDACITY



Preliminary Ideas for Future XPRIZE Competitions

AS PART OF our research process we conducted a two-day in-person workshop with 69 experts in the field of longevity, life extension and foresight. The results of this workshop included five novel ideas for a future XPRIZE competition. Their appearance in this report does not necessarily mean that XPRIZE endorses them.

COMPETITION IDEA #1:

Forever Young

THE COMPETITORS WILL develop a treatment for aging that will rejuvenate the participants by 5-10 years of age, with no longer than one year required to administer the treatment. The treatment will be administered on four cohorts: 50-, 60-, 70- and 80- year-olds, with each cohort including around 200 participants. Rejuvenation would be measured according to several different biomarkers and aging clocks.

COMPETITION IDEA #2:

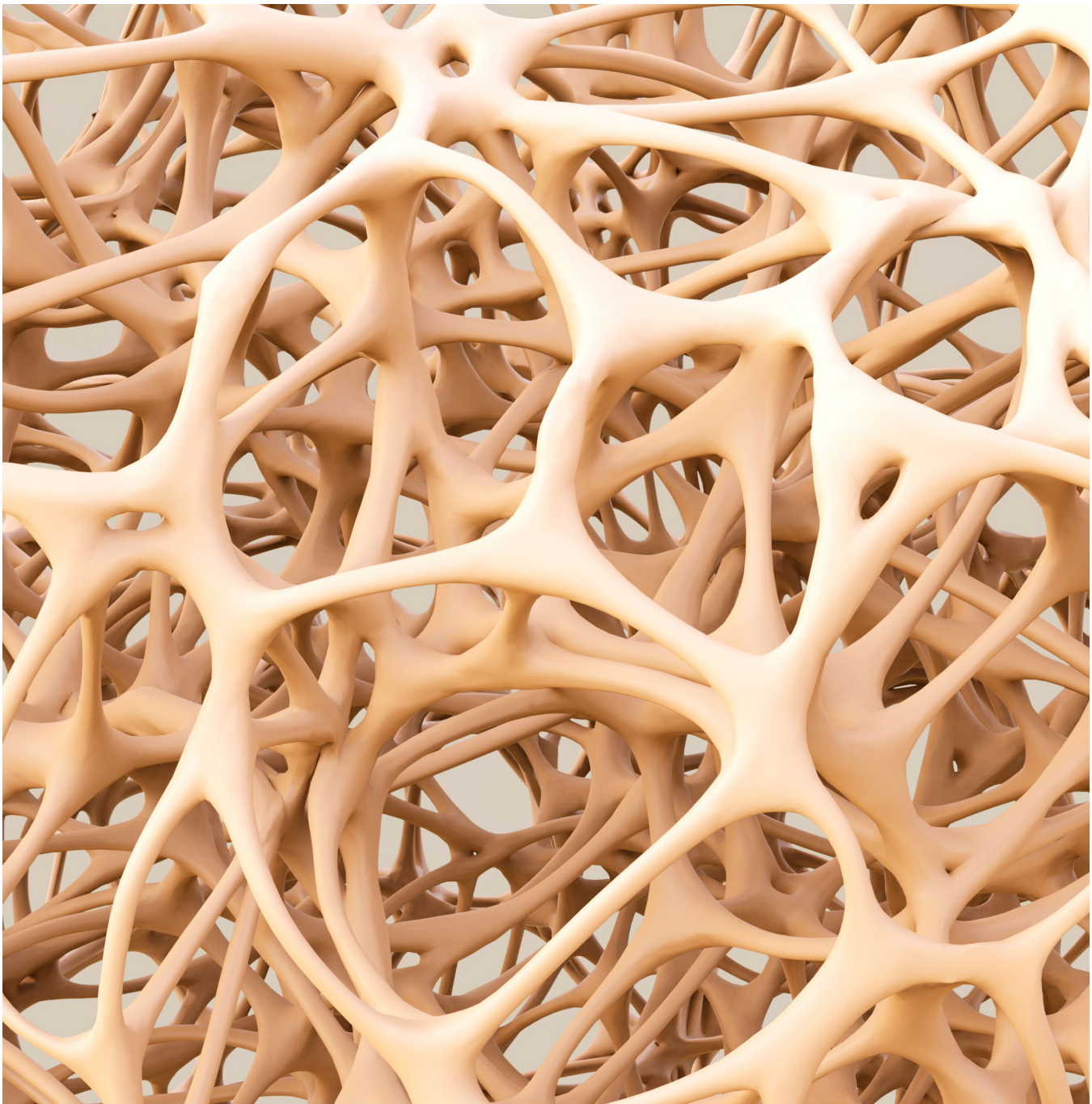
Meaningful Reversal of Dementia

THE COMPETITORS WILL develop a treatment that reverses the dementia phenotype, with clearly defined success metrics (physiological, cognition, etc.). The reversal would be demonstrated on a sufficiently large cohort of participants.

COMPETITION IDEA #3:

Restoration of Tissue Regeneration Capabilities

THE COMPETITORS WILL restore the regeneration capacity of tissues in elderly people, to the level found in younger people. The treatment will be demonstrated by rejuvenating the body's capability to handle at least one toxic condition (e.g, effects of alcohol consumption).



COMPETITION IDEA #4:

Generation and Storage of Human Organs

THE COMPETITORS WILL demonstrate a method for manufacturing personalized replacement organs for human beings. The manufactured organs should be generated from the patient's own cells, or from cells that do not lead to rejection from the transplantee's immune system. The organs should be capable of performing their normal tasks in the human body. A lab-generated heart, for example, should pump blood successfully in the body, while a lab-generated kidney should function well enough to make dialysis unnecessary.

COMPETITION IDEA #5:

Longevity Peace Prize

THE COMPETITORS WILL succeed in establishing new laws and regulations that support people's right to adapt and engineer their bodies as they like. As a direct result of the competitors' efforts, at least one major regulatory agency will acknowledge aging as a disease or a medical condition.

Envisioning the Future: Scenarios for the Year 2040

THE FOLLOWING SUMMARIZES the scenarios we created to bring to life the possible futures of longevity. We cover four distinct future scenarios—dystopian, business-as-usual, incremental, and transformative—each of which is plausible in its own way. Each scenario contains a different mixture of grand challenges that have gone unheeded as well as certain breakthroughs that have helped to mitigate them.

SCENARIO #1: THE COLLAPSED FUTURE

The global elderly population has more than doubled in proportion, with massive negative implications to society and infrastructure. Attempts to provide adequate healthcare and housing to the aging population have failed miserably. Few people believe in the concept of healthy life extension or age-reversal.

The scientific foundations necessary for achieving longevity breakthroughs are not yet successfully laid or accepted. Governments refuse to accept aging as a treatable condition, or fund research in the field in any significant way. Pharmaceutical firms generally ignore research and development in the field of life extension and age-reversal. Most aging-related diseases, including cancer, Alzheimer's, and recently discovered illnesses, remain without a cure.

SCENARIO #2: BUSINESS AS USUAL

More and more people believe that life extension and even age-reversal will become possible in a few decades. The public is therefore both aware of the potential and excited about the prospects for the future. Disagreement among the academic and medical community, however, has led to difficulties in achieving a standard set of aging biomarkers. As no robust theory of aging has been conceived, there is no holistic understanding of the aging process. Early longevity treatments are ineffective at best, or act as placebos at worst.

SCENARIO #3: INCREMENTAL CHANGE

The public is generally excited about longevity prospects, thanks to a few successful clinical demonstrations of reversing aging in tissues in human trials. These demonstrations reinvigorate funding to discover new options for regenerating or growing whole organs in the lab. However, the most advanced treatments have yet to be approved by the regulators, delaying their release into the market.

A small number of longevity treatments of limited efficacy—demonstrated in in-silico trials to extend lifespan by less than 10 years—have made it to market. Due to the scarcity of such treatments, drug providers can maintain wildly high prices, meaning they are inaccessible to most of the population. Governments are unwilling to subsidize existing treatments due to their limited impact on the conditions of aging.

SCENARIO #4: THE TRANSFORMATIONAL FUTURE

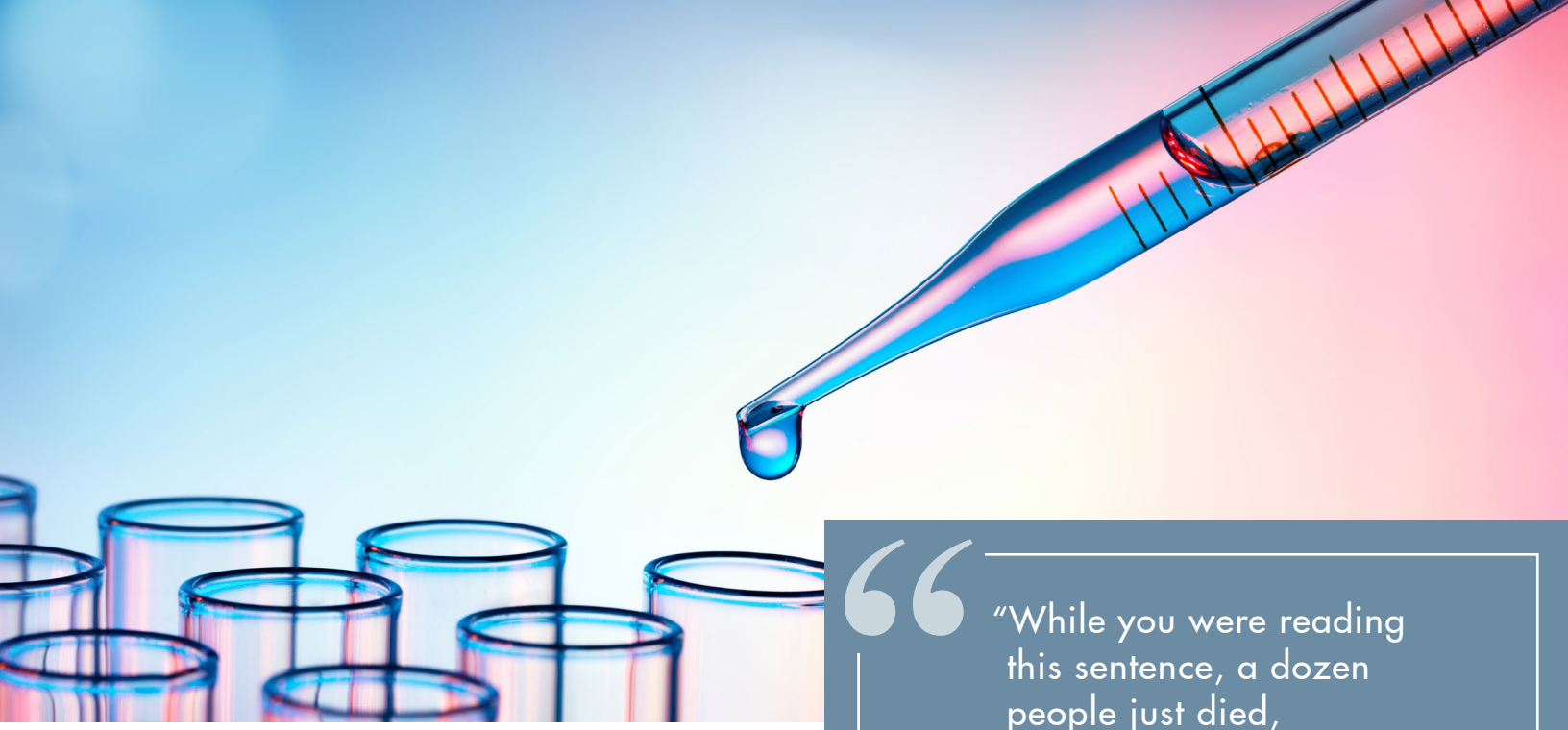
Many people enjoy the early treatments of the longevity revolution, which postpone the onset of aging-related diseases and conditions by decades. The theoretical and basic scientific understanding of aging has been mostly achieved. Schools and universities cover curriculum about healthy aging and longevity science, and the public understands the great potential of longevity research and treatment. Young and audacious innovators are encouraged to take part in the innovation of scientific processes, and their ideas can be translated rapidly into actual treatments.

Ideas for new treatments can be tested quickly and effectively on in-silico and in-vitro models, dramatically accelerating the research and development and approval processes. Powerful age-reversal and life extension treatments are still reserved for pets and farm animals but will soon be translated for human use as well. Treatment prices remain low due to fierce competition between pharmaceutical firms and governments' willingness to provide subsidies for their elderly population. Treatments are thus accessible to nearly everyone, and governmental coffers receive a net gain from the defrayed costs of extended morbidity. Geriatric clinics are increasingly transforming into youth extension clinics, and maximum lifespan has moved to 130 years, with new records expected soon.

02.

INTRODUCTION

02



> "While you were reading this sentence, a dozen people just died, worldwide. There. Another dozen people have perished. I think this is an outrage."
>
> **ROBERT A. FREITAS JR.**
> NANOMEDICINE RESEARCHER

IN THE FABLE of the Dragon Tyrant, philosopher Nick Bostrom tells the tale of a ruthless dragon that demands the lives of thousands of people every day.

"*The misery inflicted by the dragon-tyrant was incalculable. In addition to the ten thousand who were gruesomely slaughtered each day, there were the mothers, fathers, wives, husbands, children, and friends that were left behind to grieve the loss of their departed loved ones.*"[1]

Bostrom's dragon is none other than biological aging. This process, having long accompanied humanity, is accepted as natural by virtually everyone. Everybody knows they will age, and eventually die, if not due to an accident then because of some aging-related disease.

But just because this belief that human beings must age and die is so ubiquitous does not necessarily mean it is true. Science and technology have continually provided tools that can be used to achieve new wonders that would astound prior generations.

Who or what is to say that we cannot reverse, halt, or at least slow down aging, and thus also vanquish or postpone the emergence of numerous aging-related diseases that lead to so much suffering?

Doing so will not, of course, be easy. It is probably one of the grandest challenges that humanity could possibly take on. But this is where we, as XPRIZE, have an advantage.

You see: we are professional dragon-slayers.

The Woes of Aging

EVERY DAY, ROUGHLY 150,000 people die.

The reasons for their dying are varied. Some perish in violence. Others in childbirth, or a traffic accident, or from hunger. But in the developed nations, nearly 90%[2] of all deaths can be attributed to something that rarely afflicts anyone under 40: aging-related diseases—which include cancer, Alzheimer's, heart disease, diabetes, stroke, lung disease, and many others.

The death of any person is a great loss—to that person's family and friends, and to society. Worse, losing a loved one due to aging-related disease is often preceded by a prolonged period of physical and mental deterioration. This process can be emotionally devastating.

Yet the woes of aging do not end at the emotional level. The high costs of healthcare and caregiving mean that aging-related diseases are not only a personal tragedy, but an economic disaster. As an example, the American Association of Retired Persons (AARP) estimates that 40 million people in the United States provide 37 billion unpaid hours per year in family caregiving, worth $470 billion.[3] The United Nations' latest projections for the next 30 years forecast global life expectancy (at birth) to increase by roughly 4.5 years, and the number of the "oldest old" (people aged 80 and over) to triple from 143 million in 2019 to 426 million people by 2050.[4] This could spell trouble for a variety of reasons.

Aging people, for instance, often have no choice but to go into retirement because of debilitating aging-related diseases and conditions like frailty or declining cognitive function. It is no wonder, then, that pensioners comprise the lion's share of healthcare expenses.[5]

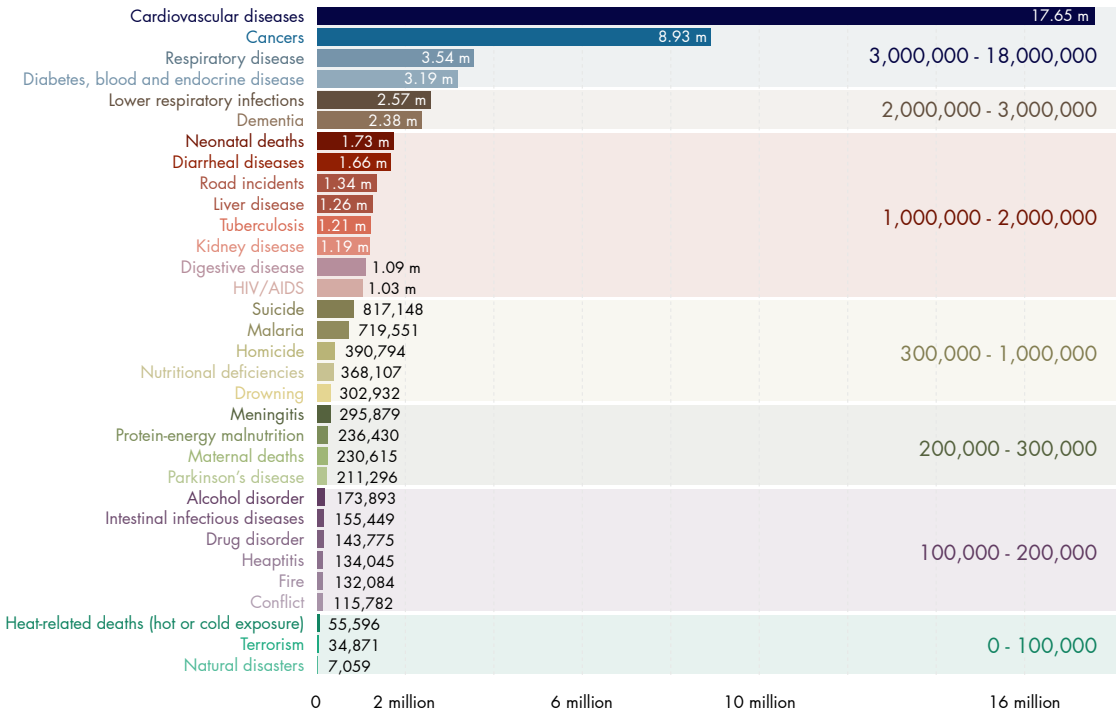
Billions of dollars have been invested in treating aging-related diseases, with very little improvement in the final outcomes.[6] These diseases are often interconnected, meaning that curing just one disease is not enough. As James L. Kirkland from the Mayo Clinic said in 2017,

"If we cured cancer, if we cured Alzheimer's disease, if we cured heart attacks and strokes, we would still die of something else a few months or a couple of years later. That's because fundamental aging processes predispose [us] to these diseases and conditions."[7]

The solution, then, is to reverse, halt, or at least slow down the aging process itself.

But is that even possible?

FIGURE 2.1: TOP CAUSES OF DEATH WORLDWIDE (2016)



Data refer to the specific cause of death, which is distinguished from risk factors for death, such as air pollution, diet and other lifestyle factors. See sources for further details on definitions of specific cause categories.

Source: Institute for Health Metrics and Evaluation (IHME); Global Terrorism Database (GTD); Amnesty International

An Interlude for Terminology

TO ANSWER THAT question, we must first distinguish a few terms.

Aging is a set of biological processes that accompany normal bodily function and lead to damage in our cells, tissues and organs that the body is not able to completely repair or remove. The accumulation of this damage leads to the development of aging-related diseases, loss of vital functions and, eventually, death.

Life expectancy, or average lifespan, is the average time a person can expect to live. Thanks to social innovations like public health and vaccination campaigns, life expectancy at birth in developed nations has been extended from 49 years at the start of the 20th century to about 76 years a mere 100 years later. These 27 extra years of life are an astounding achievement, but the maximum lifespan of the human race has barely changed over the same period.

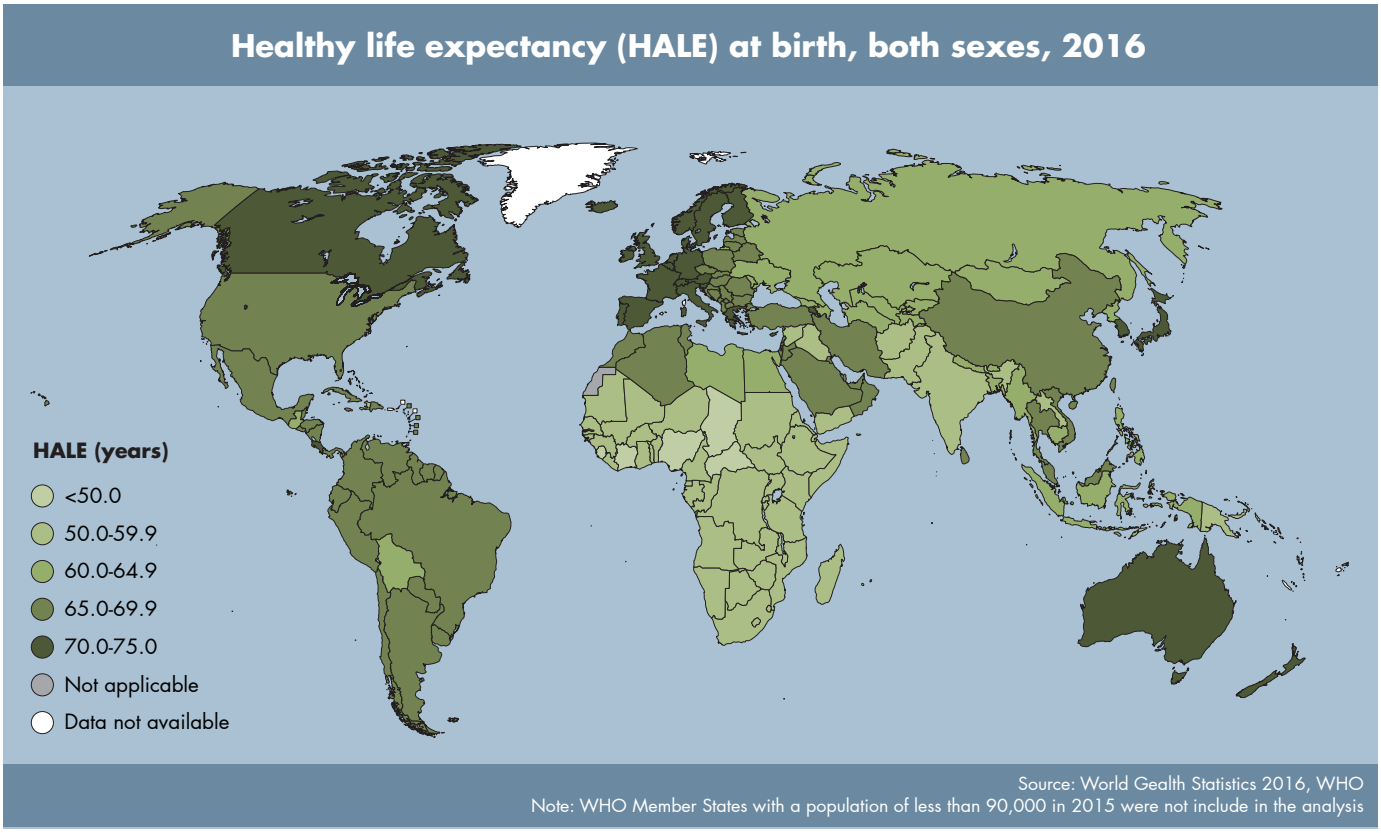
Maximum lifespan describes the maximum length of time that humans have managed to live. While science and technology have managed to vastly extend life expectancy, the same cannot be said for maximum lifespan, which is currently set at 122.[8]

Healthspan, or healthy life expectancy, describes the length of a person's life during which he or she is free from the chronic, progressive diseases of late life. It is critical to extend people's healthspan if we want to extend both quantity and quality of life. Treatments that extend healthspan will not necessarily have an effect on maximum lifespan.

Chronological age is the number of years that a person has lived. It cannot be changed as a result of any factors internal or external to the body.

Biological age is our state of health—both physical and mental. In other words, it is a measure of how far we are through our healthspan. It can be influenced by internal factors like genetics and metabolism,

FIGURE 2.2: HEALTHY LIFE EXPECTANCY AT BIRTH, BOTH SEXES (2016)



> "The day before something is a breakthrough it's a crazy idea."
>
> **PETER DIAMANDIS**
> XPRIZE FOUNDER

and external ones like lifestyle choices, physical activity, and sleeping habits.

Life extension treatments extend people's life expectancy. It is possible—some say certain—that life extension treatments will only achieve their effect as a result of extending healthspan, that is, by postponing the emergence of aging-related diseases and their consequences. The most powerful life extension treatments should also increase people's maximum lifespan.

In this report, when we refer to increasing human *longevity,* we mean spreading the opportunity around the world for a longer and healthier life. In other words, we focus on increasing both lifespan and healthspan—not only because merely extending one's "frailspan" (the period of life beyond one's healthspan) is of questionable value, but because increasing longevity may only be possible by extending healthspan.

Note: when we examine treatments for increasing longevity, we concentrate on those that affect the last few decades of human life (rather than increasing longevity by preventing child mortality, for example). Some of these may eventually extend maximum lifespan. Several treatments or breakthroughs discussed in this report also examine *age-reversal*, which aims to effectively turn back the clock on biological age by rejuvenating cells and tissues. While this achievement may sound fantastical to some, partial age-reversal has already been achieved in animal experiments, and it may be only a matter of time until science and technology allow for the transfer of these interventions to people.

But Should Aging Be Stopped?

SHOULD WE EVEN try to stop the aging process? We accept that this is a debatable question. Below, we briefly address some of the most common arguments against fighting aging.

"Aging is natural, and should therefore not be interfered with"

Just because something is "natural" does not mean it is necessarily good; the HIV virus is also natural, as is appendicitis. Furthermore, immortality or very long lifespans can also be natural: some species of jellyfish seem to be immortal, sharks can achieve lifespans of centuries, and trees can live for thousands of years. Additionally, even if one considers lifespan extension as something unnatural and thus undesired, one should consider that humans display many unnatural habits, like playing piano, indulging in mathematics, using antibiotics and flying around in airplanes.

Aging is the underlying cause of numerous chronic diseases, and in order to effectively cure them, methods must be developed that address aging directly. As long as human beings have existed, we've focused on tackling barriers that jeopardize our health and happiness. XPRIZE believes in first-principles thinking, and since there is no scientific proof that aging and aging-related diseases and conditions are inevitable, we wholeheartedly believe in the legitimacy of this work.

"Aging should not be eliminated, since the world would then suffer from overpopulation"

While the world's population is already increasing, growth rates differ across the globe. According to the UN's 2019 population report, by 2050 the population of sub-Saharan Africa is expected to double, while over the same period 55 countries

LONG-LIVING ORGANISMS

The world is full of plants and animals that live for a much longer time than what we may consider a "normal" lifespan. What lessons might we be able to decipher from these resilient organisms?

Geoduck Clam:
150 years[9]

Bowhead Whale:
200 years[10]

Greenland Shark:
200-500 years[11]

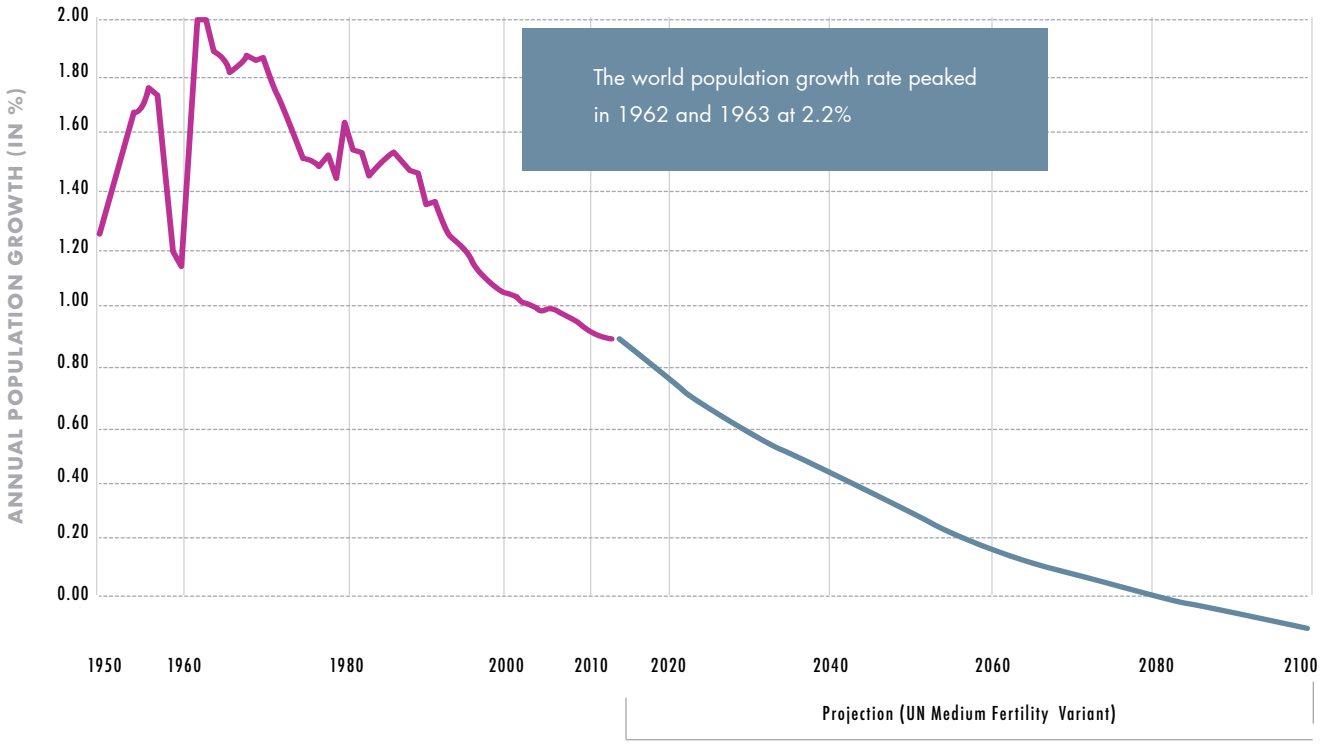
Baobab Tree:
2000+ years[12]

Glass Sponge:
11,000 years[13]

Hydra:
Immortal?![14]

FIGURE 2.3: ANNUAL WORLD POPULATION GROWTH RATE (1950-2100):

Sources: Observations: US Census Bureau & Projections: United Nations Population Division (Medium Variant (2015 revision)



or areas are projected to experience population declines. This reduction is primarily due to low levels of fertility, and, in some places, high rates of emigration. [15]

There is no clear evidence that increasing longevity would lead to overpopulation. In fact, there is good evidence that families in developed nations tend to be smaller, in part because women there tend to have fewer children than in developing nations. As global poverty falls and availability of contraception rises, world population will likely increase in the near-term, but growth rates are expected to shrink, in line with historical trends (see Figure 2.3).

Even if parents were to keep bringing children into the world at current rates, overpopulation would not be inevitable. Concerns about overpopulation have existed for at least the past two hundred years, yet time after time such forecasts are proven overly pessimistic. They do not adequately account for human ingenuity and the ability of science and technology to improve the efficiency and effectiveness of how we use the Earth's resources.

No reasonable forecast has yet been made about Earth's "carrying capacity." Meanwhile, it is undeniable that aging and aging-related diseases impose a very real burden on society, the economy, and the Earth, and therefore require innovation.

"Life extension treatments will only be available to the affluent and the powerful"

Life extension treatments must indeed be accessible to all who wish to use them. While some treatments may be expensive at first, history teaches that their cost and price will be dramatically reduced in just a decade or so, once patents expire, competition increases, and/or the underlying technology advances. Moreover, some potential interventions against aging based on inexpensive generic drugs (e.g., metformin, doxycycline, fisetin and others) could quickly become widely available once their beneficial effects on healthspan are proven. Additionally, if the value of treatments is demonstrated, governments could intervene to promote accessibility, whether for economic or humanitarian reasons.

"Living longer will be too expensive"

The concern that living longer would impose an unbearable financial cost on

older individuals is based on the preconception that aging is associated with frailty and other conditions that keep older adults from being productive. If, however, living longer were to mean a longer healthspan, then the cost of living at an old age should not be any more burdensome than living at the age of 30, 40, or 50.

"More old people will be a burden on the healthcare system"

In medicine, prevention is considered a more cost-effective approach than responding to the progression of a chronic disease. This explains why the World Health Organization is focusing the efforts of local governments on reducing the risk factors of chronic diseases, which comprise the main burden for healthcare systems worldwide.

Indeed, chronic diseases like heart disease cost the U.S. $199 billion a year, while cancer and diabetes cost $174 billion and $237 billion respectively.[16] A recent study of the U.K.'s elderly social care system released findings that the number of people over 85 years of age with high levels of dependency on social care assistance will nearly double by 2035. Should the world continue to do little to address head-on this problem of rising life expectancy coupled with persistent multiple chronic diseases, such statistics will carry grave implications for the future of health and social care services for the aging population at a global scale.[17]

Given that life extension treatments are meant to increase healthspan and decrease the length of the unhealthy period of life (thereby promoting what is often called a "compressed morbidity"), the burden on the healthcare system should not increase and could in fact be significantly alleviated.[18]

"Nobody wants to live longer if that just means being sick for a longer time"

Indeed! Thus the focus must be on extending healthspan—the length of time someone is free of aging-related diseases and conditions—in addition to lifespan. As mentioned, extending lifespan may only be possible by extending healthspan—and the best way to extend the disease-free period of life is to address the aging process itself.

"People won't want to live longer even if they're healthy"

Some people won't want to live longer, for reasons that could range from personal to religious or ideological. The right to choose whether one receives life extension treatments, once they are developed, is a crucial consideration. Encouragingly, surveys from several developed countries show that when perfect health is part of the equation, somewhere between one-third to two-thirds of participants indicate the desire to live much longer.[19]

"Life has no meaning without death"

It is certainly possible that death gives meaning to life for some, but there is no scientific evidence that people cannot adapt to living without the constant threat of death and debilitating aging-related diseases hanging over them.

"There won't be as much dynamism of ideas"

Many are concerned that in a society where death is less common, the turnover and development of ideas would become more stagnant. Similarly, some fear that longer lifespans would enable tyrants to remain in power much longer. We suggest that instead of relying on random natural death to correct for these issues, society ought to install and uphold rules and regulations to prevent leaders from staying in positions of power for too long, and thereby enable an environment that encourages a dynamism of ideas. Also, longer lifespans would enable great artists, scientists and activists to share the fruits of their intellect and endeavours with society for a longer time.

Indeed, a world of longevity could bring wonders for countless generations to come. We invite the reader to join our journey and explore the possibilities of this Future of Longevity in the following pages.

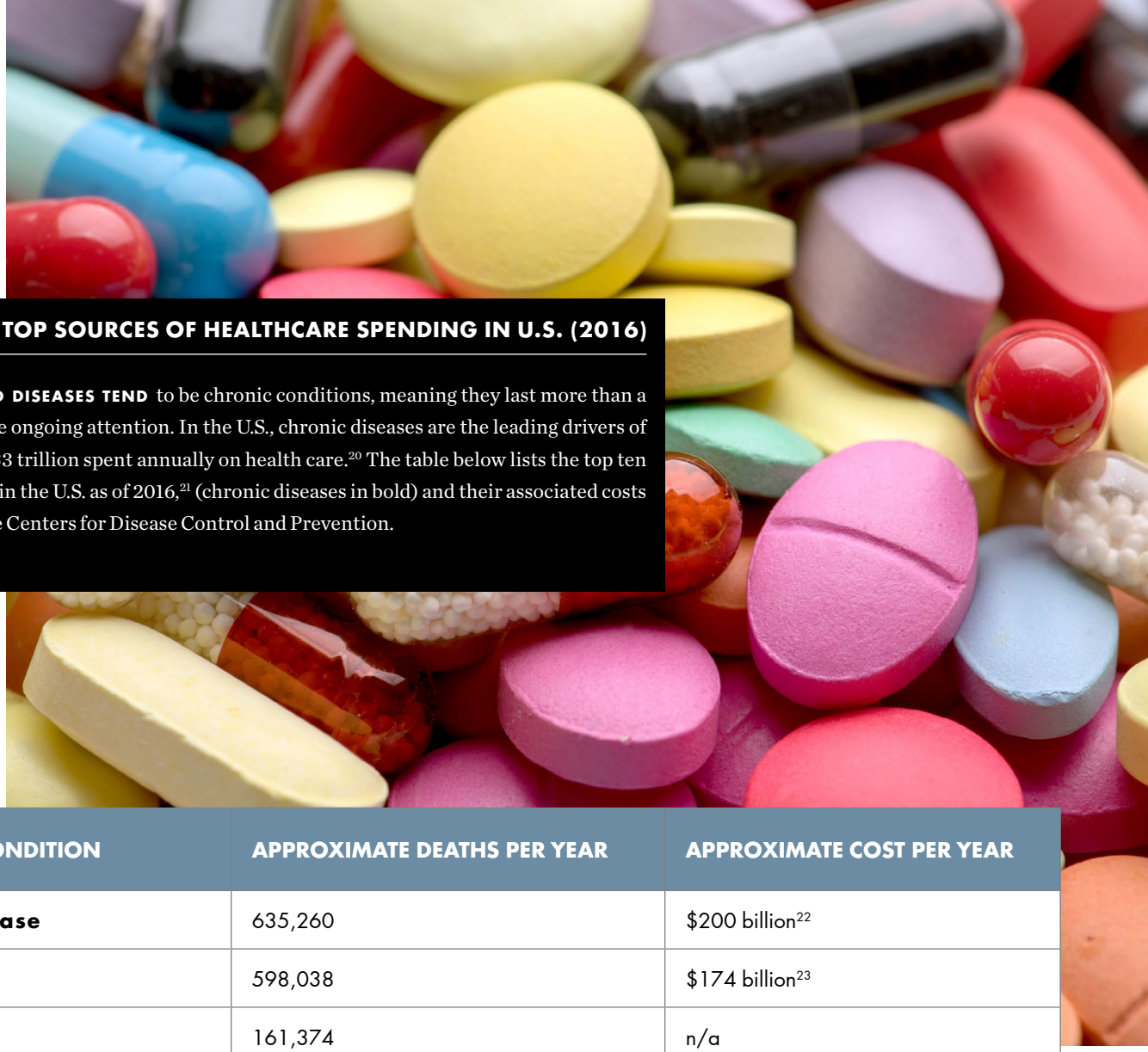


FIGURE 2.4: TOP SOURCES OF HEALTHCARE SPENDING IN U.S. (2016)

AGING-RELATED DISEASES TEND to be chronic conditions, meaning they last more than a year and require ongoing attention. In the U.S., chronic diseases are the leading drivers of the more than $3 trillion spent annually on health care.[20] The table below lists the top ten causes of death in the U.S. as of 2016,[21] (chronic diseases in bold) and their associated costs according to the Centers for Disease Control and Prevention.

DISEASE/CONDITION	APPROXIMATE DEATHS PER YEAR	APPROXIMATE COST PER YEAR
Heart Disease	635,260	$200 billion[22]
Cancer	598,038	$174 billion[23]
Accidents	161,374	n/a
Lower Respiratory Disease	154,596	$36 billion[24]
Cerebrovascular Disease	142,142	$34 billion (stroke only)[25]
Alzheimer's Disease	116,103	$159 billion - $215 billion[26]
Diabetes	80,058	$237 billion[27]
Influenza and Pneumonia	51,537	$8.7 billion[28]
Kidney Disease	50,046	$79 billion[29]
Suicide	44,965	n/a

03.

OBSTACLES TO A PREFERRED FUTURE OF LONGEVITY

03

Methodology

Fashion & Social Obstacles

Commerce & Economy Obstacles

Government & The Law Obstacles

Cultural & Ethical Obstacles

Natural Obstacles

Methodology

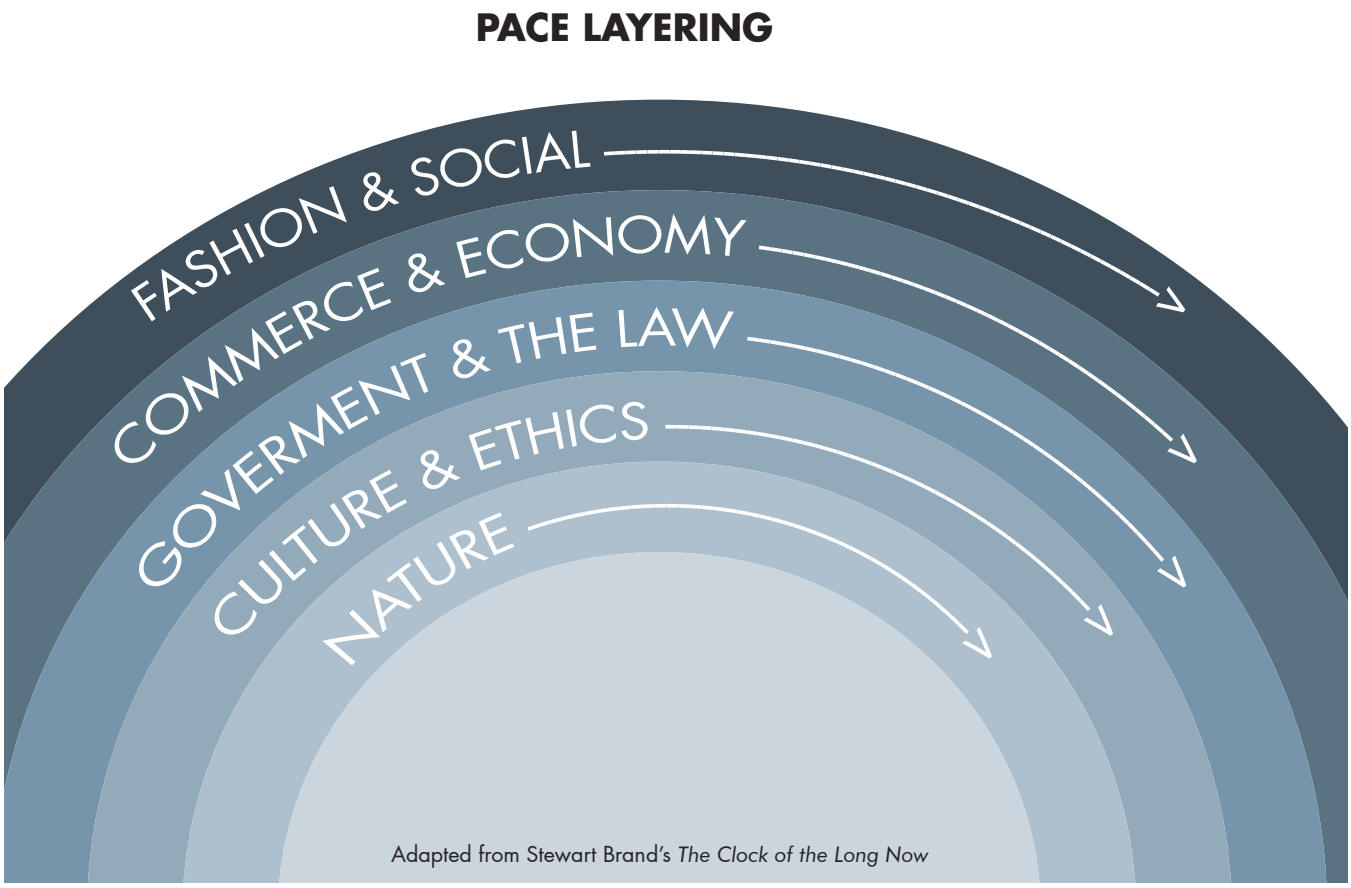
IN THIS SECTION we identify the main obstacles standing in the way of the vision we've outlined in the Preferred Future Statement. These obstacles are arranged according to a variation on the pace-layer analysis system originally conceived by Stewart Brand in his book *The Clock of the Long Now*.

In pace-layer analysis, the driving issues and forces are grouped into several layers, each of which is changing at a different pace. The original pace-layer schematic proposed by Brand contained six layers. From the most rapidly changing to the slowest, these were: fashion, commerce, infrastructure, governance, culture and nature.

For the Future of Longevity Impact Roadmap research, we chose to reformulate the schematic into the following layers, from fastest to slowest:

- **FASHION & SOCIAL**
- **COMMERCE & ECONOMY**
- **GOVERNMENT & THE LAW**
- **CULTURE & ETHICS**
- **NATURE**

PACE LAYERING



WANT TO JUMP STRAIGHT TO THE BREAKTHROUGH SOLUTIONS? TURN TO PAGE 200 TO EXPLORE THE GAME-CHANGERS WE'VE IDENTIFIED THAT COULD SIGNIFICANTLY ACCELERATE THE FIELD OF LONGEVITY.

Layer 1: Fashion & Social Obstacles

Misinformation About Longevity Treatments

SUMMARY

PEOPLE ARE OFTEN exposed to misinformation about a variety of health-related topics, such as vaccines, genetically modified organisms (GMOs), and blood transfusions. As the concepts of slowing down or reversing aging take root, there are bound to be those who will spread misinformation about legitimate treatments, whether to sell their own unproven treatments or otherwise. Also, the perpetuation of unfounded fears of new therapies that can delay aging, like gene editing or stem cell therapy, could hamper their development.

DESCRIPTION

Misinformation about medical treatments often spreads in online discussion forums and blogs and can be exacerbated by online "trolls" and automated bots.[30] Even some reputable publications may give space to misinformation on a variety of topics, including the alleged dangers of genetically engineered plants or promises about magic cures that can only be found in unregulated offshore clinics.[31]

Misinformation is often shared by people who genuinely believe it. Some kinds of misinformation, however, can also bring profit to individuals and organizations. Many websites, for instance, spread misinformation about the dangers of certain mainstream medications, while hawking their own unproven wares.[32]

IMPACT

Misinformation about life extension treatments could discourage uptake. It could also sway public opinion and legislation, much in the way that legality of genetically engineered plants has largely been shaped by misinformation.[33]

Conversely, misinformation could also make some alleged life extension treatments appear more legitimate than they are. Such cases may disillusion the public, as people grow tired of false promises and choose to ignore new developments in the field of longevity.

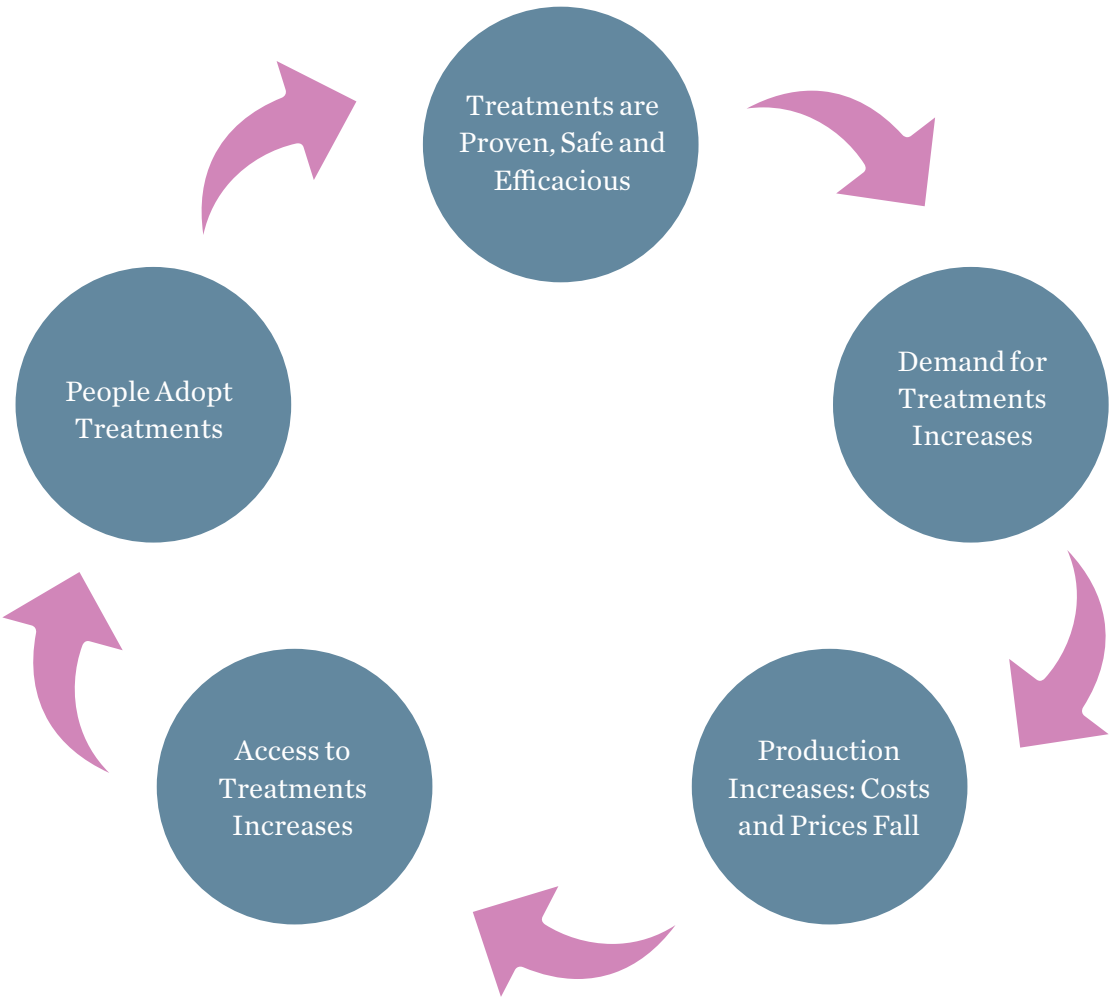
DIFFICULTIES

It is often difficult for the layperson (and sometimes even for experienced scientists) to distinguish between scientifically valid news and misinformation. Especially in this era of increasingly abundant information, it is important to insist on rigorous scientific tests, peer review and other methods to separate untruths, half-truths and straight-out lies from real scientific news and knowledge.

WHY DOES PUBLIC PERCEPTION MATTER?

PEOPLE CAN INFLUENCE the trajectory and progress of the longevity movement in several ways. The public has the power to impact how longevity is legislated by their governments —for example, whether aging is legally classified as a treatable condition, or how much money is allocated for scientific research (see Government & Law Obstacles, on Page 68). Participants for clinical trials are also needed to demonstrate the efficacy and safety of longevity treatments. Only if people actually begin to use longevity treatments can global accessibility grow: when demand for longevity treatments is high, costs and prices will fall, due to market forces and/or governmental intervention. This virtuous cycle is outlined below in Figure 3.1.

FIGURE 3.1: THE VIRTUOUS CYCLE OF ADOPTION



Concern of Overpopulation Straining Earth's Resources

SUMMARY

A COMMON CONCERN about increased longevity is that Earth won't be able to sustain a swollen population with its finite supply of resources. Regardless of the veracity of this concern, its impact on public perception affects progress.

DESCRIPTION

Fears of overpopulation have existed for hundreds of years. The idea that Earth has a "carrying capacity" was perhaps most famously championed by Thomas Malthus in the late 18th century. Malthus claimed that since human population grows exponentially but food production increases linearly, overpopulation is inevitable. Any attempt to escape this overpopulation, he claimed, is futile: "man cannot by any efforts of reason escape from it." [34]

Several books espousing similar ideas were published and widely read in the 20th century, perpetuating Malthus's scarcity mindset.[35] Although the logic behind these pessimistic prophecies has been challenged by numerous innovations that have made resources more abundant,[36] fears of overpopulation persist among the public as well as the scientific community.[37]

These fears can be categorized into first-order and second-order consequences of human population growth. First-order consequences include an insufficient supply of water, food, energy, farmable land, and minerals.[38]

The presumed results of these first-order consequences are the second-order consequences. As Hendrixson and Hartmann and others[39] have written, these include:

- Environmental deterioration, including the acceleration of climate change
- Economic stagnation & massive poverty
- Violent competition for resources
- Mass migration to more resource-rich regions
- Social and political unrest

IMPACT

Whether or not these concerns are legitimate, the fear of overpopulation is real. This fear may limit research and development funding (especially from public sources), research trial participation, and adoption of longevity interventions and treatments.

DIFFICULTIES

The widely-held paradigm of scarcity is difficult to dispel among the general public, and even among policy- and decision-makers. Furthermore, overpopulation—taken on its own and disconnected from the possibilities of continuous scientific and technological progress—is a justifiable concern about the future. This issue, then, must be treated seriously in order to avoid both the common fears about overpopulation, and the chance that it may actually come to pass.

Layer 2: Commerce & Economy Obstacles

Slow Pace of Drug Development and Approval

SUMMARY

NOVEL AND INNOVATIVE therapeutics and treatments will need to be developed and approved in order to slow and/or reverse the aging process. Such therapies, however, tend to take a long time to be discovered, developed and approved, and many will fail at some point in the process. With such low chances of success and high stakes for research and development, the journey to new therapeutics is bound to be slow.

DESCRIPTION

As of today, as the U.S. Food and Drug Administration (FDA) goes, so goes the worldwide regulatory environment. Under the FDA, the drug development process comprises multiple steps, each of which requires time, effort, and significant monetary investment.[40]

Once a certain drug candidate has been identified in the lab, usually following testing on animals, it goes through four phases of clinical trials, detailed in Figure 3.2.

Final numbers vary depending on the drug candidate and its target, but on average only 5.2% to 13.8% of all candidates that enter Phase 1 end up being approved.[41] The first three phases combined tend to require 6-7 years from start to finish, followed by another 0.5-2 years for FDA review and for manufacturing to start. Phase 4 can take up to 10 years.[42]

One additional complexity, which applies specifically to life extension drugs and therapies, is that the endpoint to measure the effect of a given treatment for human lifespan is the moment of death. To identify the ultimate results of a certain intervention, then, one has to wait until the participants in the clinical trial start to die.

FIGURE 3.2: 4 PHASES OF CLINICAL TRIALS*

PHASE 1	PHASE 2	PHASE 3	PHASE 4
The candidate is tested on healthy individuals to determine its safety. About 39% of all candidates pass this phase.	The candidate is tested on a small number of sick patients to assess its efficacy and side effects. About 32% of the remaining candidates move on to the next phase.	Trials are conducted on a large number of patients. About 60% of remaining candidates make it through this stage.	By this time the drug candidate has been approved for marketing and is regularly used by thousands of volunteers subject to ongoing surveillance to identify any side effects that weren't evident in the previous phases.

*Success rates are calculated as a weighted average of the figures reported from Wong et. al's 2018 paper.[45]

IMPACT

Since the pace of new drug development is so slow and fraught with failure, new medications take a long time to reach the market. Additionally, the high development costs and the need to compensate for past failures force pharmaceutical companies to charge large sums for the medications that make it to market. Thus, even if a successful anti-aging treatment were to be developed, it would probably be accompanied by a hefty price tag that would keep the medication out of the hands of many.

While regulators are often blamed for slowing innovation, in this case they arguably perform admirably well. The FDA aims to finish its review within 8-10 months, which could be considered defensible given that its scientists must review the results of several clinical trials and produce a 200-page report. The European Medicines Agency (EMA), for its part, similarly requires around six months to assess new submissions.*[43]

DIFFICULTIES

A key difficulty behind this obstacle is that the science underlying aging-related diseases (and diseases in general) is complex and not yet fully understood. The unfortunate implication is that pharmaceutical firms cannot forecast with sufficient accuracy whether a certain therapeutic candidate will achieve success or not, nor what kind of side effects it may carry, which disincentivize their innovation in the space.[44]

Additionally, there are currently few if any good models of human tissues for testing new drugs in the lab. This may account for the fact that just over 19% of all candidate drugs successfully pass Phase 2, in which they're tested for efficacy in human beings.

*Note: time estimates were based on research that looked specifically at cardiorenal trials; there may be considerable variation across trial types.

Accessibility of Treatments

SUMMARY

A MAJOR ISSUE regarding longevity treatments is whether they will be accessible to all. Medicines today usually have a high price because of expensive development processes and patent dynamics. It is therefore unclear if the current healthcare systems can provide future longevity treatments on a global scale. As with many social concerns related to longevity, even if this one is dubious, its persistence poses a real obstacle.

DESCRIPTION

Broad accessibility should be one of the basic requirements for any proposed treatment. Providing future treatments for the masses, however, could be difficult for affordability reasons. Healthcare costs are rising all over the world. Current spending on public health and long-term care in OECD countries and the BRIICS (Brazil, Russia, India, Indonesia, China and South Africa) stands at 6% of GDP, with considerable variation across countries.[46] Much of the anticipated growth of this figure is driven by the surge in elderly people: it is predicted in the U.S., for example, that by 2029, 71.4 million people or 20% of the total national population will be aged 65 years or older, up from 14% in 2012[47] (the first cohort of Baby Boomers, or those born between 1946-1964, first turned 65 in 2011[48]). In addition, the 65 and over population spends about three times more on personal health care than that of a working aged person[49]. As a result, healthcare expenses among the same cross-section of countries are expected to reach 9.5% of GDP by 2060, in a cost-containment scenario.[50]

Forecasts are particularly alarming in the U.S., where the Congressional Budget Office has projected that government programs supporting public health will cost up to 10.4% of GDP by 2037[51]. Already, healthcare costs are the second leading cause of stress for Americans, with 17% incapable of paying for routine healthcare expenses.[52]

Given that such expenditures directly correspond to affordability and therefore accessibility, the ongoing ballooning of costs must be addressed in order to allow for longevity treatments to reach as many people as possible. As expressed by Steven Austad, scientific director of the American Federation for Aging Research, "If you demonstrate that these drugs work, probably everybody is going to want to take the drugs. So then the question becomes a question of cost."[53]

Some generic drugs that are currently used for specific aging-related diseases but which also hold potential for extending healthspan face a separate set of bottlenecks. Namely, these drugs (e.g., metformin, doxycycline, sartans, statins, and others) do not offer great economic incentives for large-scale production.

> "I would like to see a society with a prospering economy because of a growing healthy population, as opposed to the current situation where prosperity is linked to the growing 'market' of chronically-ill citizens. Longevity with chronic illness from cradle to grave is the ideal scenario for pharma."
>
> **DR. YOAV MEDAN**
> FUTURIST

FIGURE 3.3: PERCENTAGE OF POPULATION AGED 65 OR OLDER

REGION	2019	2030	2050	2100
World	**9.1**	**11.7**	**15.9**	**22.6**
Sub-Saharan Africa	3.0	3.3	4.8	13.0
Northern Africa & Western Asia	5.7	7.6	12.7	22.4
Central & Southern Asia	6.0	8.0	13.1	25.7
Eastern & South-Eastern Asia	11.2	15.8	23.7	30.4
Latin America & the Caribbean	8.7	12.0	19.0	31.3
Australia/New Zealand	15.9	19.5	22.9	28.6
Oceania (excluding Australia & New Zealand)	4.2	5.3	7.7	15.4
Europe & Northern America	18.0	22.1	26.1	29.3
Least developed countries	3.6	4.2	6.4	15.3
Land-locked Developing Countries (LLDC)	3.7	4.5	6.4	16.8
Small Island Developing States (SIDS)	8.7	11.9	16.1	23.7

Source: United Nations, Department of Economic and Social Affairs, Population Division, World Population Prospects 2019

IMPACT

The issue of accessibility troubles many and may pose a barrier to progress in the longevity field if it sours public opinion. Future healthcare costs are a major source of concern for governments. Demand for longevity treatments will be high, so the costs to government of subsidizing such treatments could be massive—though if such treatments extend healthspan, the net healthcare costs would likely shrink, given that most of the current healthcare expenditure is spent on elderly patients with extended periods of morbidity.[54]

DIFFICULTIES

It is difficult to make a treatment highly accessible in the current pharmaceutical-centric ecosystem, especially in the U.S., where the efficiency of the healthcare system is often subject to severe criticism.[55] At least in the case of therapeutic non-biological drugs, costs—and therefore prices—tend to be high because of the time, resources, and frequent failures involved in the process of bringing medications to the market, in addition to governmental regulations that allow for temporary monopoly power. Barring improvements in the research and development process and changes to the regulatory system, these drivers will continue to impose barriers to accessibility.

Another difficulty regarding accessibility is the distribution of treatments to developing regions, which tend to be far from the center of western pharmaceutical companies and their manufacturing facilities. It is likely that if longevity treatments are to be truly accessible to all, a complex delivery system must be developed in order to supply even the remotest villages.

Layer 3: Government & The Law Obstacles

Governments Don't Classify Aging as a Treatable Condition

SUMMARY

THERE HAVE BEEN few attempts to persuade the government to classify aging and its complications as a treatable condition. This leads to a lack of funding for appropriate treatments, and greater difficulty in researching, developing and prescribing medication that could mitigate the aging process.

DESCRIPTION

Governments and international organizations like the World Health Organization by and large don't consider old age and its complications a treatable condition. The consequences of this choice manifest in several ways. Sarcopenia (loss of muscle mass), for example, is well known to occur during aging, with a 2-3% annual loss of skeletal muscle strength.[56] The disorder, however, is not recognized by the FDA as a treatable indication nor does the FDA provide any general criteria that can assess treatments that might slow the aging process.[57] As a result, the agency has yet to approve any medication that targets aging itself.[58]

Some recent developments indicate that change is coming on this front. The FDA's preliminary approval of the TAME (Treating Aging with Metformin) trial, for instance, suggests that governments may be growing more open to treatments that target aging directly.[59] Similarly, the World Health Organization has recently defined a new class of "aging-related" diseases.[60] While these developments are encouraging, governments and international organizations can do much more to focus attention—and funding—directly on the aging process.

> "A doctor sees old people who are shrinking and getting weak, but there is no medical terminology that's been created and made uniform to allow the doctor to make a diagnosis, look at possible causes, and make a treatment plan. "
>
> **DR. STEPHANIE A. STUDENSKI**
> PROFESSOR OF MEDICINE AT THE UNIVERSITY OF PITTSBURGH[62]

IMPACT

Under the current paradigm, pharmaceutical and startup companies working on treatments for aging are forced to target an indication that addresses a specific aging-related disease (e.g., cardiovascular disease, osteoporosis, macular degeneration, hearing loss) rather than targeting the aging process itself. In the words of Dr. Christoph Westphal, "Curing aging is not an endpoint the federal drug agency would recognize."[61] This results in research and development efforts being focused further downstream than the underlying aging process. The situation also limits physicians' ability to prescribe certain drugs to their patients, since one cannot treat a disease that does not officially exist.

DIFFICULTIES

As a medical discipline, finding solutions for aging often struggles to achieve widespread legitimacy. This perpetuates the view of the FDA and other governmental authorities that aging is not a treatable condition. A vicious cycle ensues, wherein funding in the field is relatively low, which contributes to slow progress, which justifies the limited funding, and so on. The recent development of the introduction of the special code "Aging-related" into the ICD-11 represents progress, but much remains to be done before considering the problem solved.

Governments Will Face Difficulties with Current Pension Laws

SUMMARY

AS MORE PEOPLE reach the retirement age and live for a longer duration thereafter, pension bills will become too expensive for society. Pension laws—which were created in the 19th century—will have to be altered, but this is a colossal and hazardous endeavor for governments to undertake..

DESCRIPTION

People are living longer today than ever before. The average life expectancy of 65-year-olds in the U.S. has grown since 1940 from 76.9 for men and 78.4 for women to 83.1 and 85.6 in 2018, respectively—meaning six to seven more years of life.[63] Retirement benefits, however, generally continue to be handed out at the same, relatively young age of 65, with an attached cost of nearly $860 billion in 2015, and rising every year. If life expectancy continues to increase, so will the burden of retirement payments.

The U.K., for its part, is in similar straits, with a $4 trillion retirement savings deficit. This figure is forecast to rise by 4% annually, reaching $33 trillion by 2050.[64] Switzerland experiences the same trouble. In 1948, for each Swiss pensioner there were seven people working. By 2016, there were only 3.4 Swiss workers per Swiss pensioner,[65] and by the end of the 21st century this ratio is expected to drop to just two workers for every pensioner. A similar worsening in this so-called "dependency ratio" is evident all over Europe and in several nations in Asia, as well.[66]

Such developments should have led to a revision of pension laws, but these laws are notoriously difficult to change. As a result, governments and the public do have a reason to fear further increases in life expectancy, since in the absence of change it will also increase the financial burden incurred by the younger generations. The Japanese government, for instance, estimates that an average pensioner couple will receive benefits equal to approximately half the income of a younger, working person. This situation will obviously be difficult to sustain for long, even under the most optimistic economic projections.[67]

FIGURE 3.4: AVERAGE LIFE EXPECTANCY OVER TIME

AVERAGE LIFE EXPECTANCY

Calendar Year	Historical Data			
	At Birth		At Age 65	
	Male	Female	Male	Female
1940	61.4	65.7	11.9	13.4
1945	62.9	68.4	12.6	14.4
1950	65.6	71.1	12.8	15.1
1955	66.7	72.8	13.1	15.6
1960	66.7	73.2	12.9	15.9
1965	66.8	73.8	12.9	16.3
1970	67.2	74.9	13.1	17.1
1975	68.7	76.6	13.7	18.0
1980	69.9	77.5	14.0	18.4
1985	71.1	78.2	14.4	18.6
1990	71.8	78.9	15.0	19.0
1995	72.5	79.1	15.4	19.0
2000	74.0	79.4	15.9	19.0
2005	74.8	80.0	16.7	19.5
2010	76.1	80.9	17.6	20.2
2011	76.2	80.9	17.6	20.2
2012	76.3	81.0	17.7	20.3
2013	76.3	81.0	17.7	20.3
2014	76.3	81.1	17.8	20.4
2015	76.1	81.0	17.8	20.3
2016	76.0	81.0	17.9	20.5
2017	76.4	81.1	17.9	20.5
2018	76.5	81.3	18.1	20.6

Source: U.S. Government Publishing office, The 2019 Annual Report of the Board of Trustees of the Federal Old-Age and Survivors Insurance and Federal Disability Insurance Trust Funds

IMPACT

This situation could result in governments cutting into retirees' pensions and benefits, leaving many elderly people despondent and potentially incapable of taking care of themselves. It could also lead to a new zeitgeist in which the elderly feel they have no right to go on living for decades after their retirement, while spending the money of their nation's young and working people. One more negative consequence is the recent tendency of some governments to save money by cutting subsidies for medical services and nursing support for old people.[68]

DIFFICULTIES

It is difficult for governments to change retirement laws and raise the retirement age, as evidenced by the fight over raising the retirement age in the U.S. and Switzerland. The public often objects to such raises, resulting in less enthusiasm from the people empowered to make changes.

Layer 4: Cultural & Ethical Obstacles

Ideological Objections

SUMMARY

PEOPLE MAY RESIST longevity treatments, for themselves and/or for society, due to objections grounded in various forms of ideology.

DESCRIPTION

Ideological objections to longevity can be grouped into three categories according to their source: religion, appeal to nature, and fear of the unknown. In addition to longevity-specific objections it is useful to consider objections that have been raised against related subjects, including vaccines, genetically-modified organisms (GMOs), abortion, and human enhancement.

Religion

A key tenet underlying the opposition by various religious groups to human enhancement and radical life extension is the shared idea that humans are made "in their Creator's image"[69]. Some religious movements view changing the basic nature of a human as a perversion of this image and thus a violation of religious doctrine.[70] Regarding human body interventions, some theologians distinguish between a therapy and an enhancement—a therapy responds to a disease or accident and thus, so the theory goes, restores a person's godly image, whereas an enhancement is thought to pervert it.[71]

Similarly, the use of biotechnology to enhance human vitality is viewed by some religious thinkers as an unholy act of "playing God" or as a profane influence on the way things are supposed to be.[72]

Religious objections may also appeal to the materials that comprise longevity treatments. For example, treatments that use human placenta or animal gelatin material may be rejected because they violate tangential religious laws.[73]

Appeal to Nature

Studies show that even among the non-religious there often exists a feeling that nature is "created".[74] Researchers suggest this is rooted, at least in part, in the human teleological mindset that inclines us to think that nature and the universe must have an intended purpose. Human beings are also inclined toward psychological essentialism, a way of apprehending the world that entails ascribing certain unobservable but inherent characteristics to what we perceive: for example, the unfalsifiable idea that humanity itself has some essential "nature." Such perceptions are instilled over long periods of time through evolved cognitive biases and cultural socialization.[75]

One of humanity's most deeply ingrained narratives is that contravening this nature may carry substantial unforeseen consequences. Adam and Eve ate the fruit of the Tree of Knowledge to gain awareness but were expelled from paradise. Icarus made wings to soar above the clouds but flew too close to the sun and lost his life. Dr. Frankenstein built a superhuman to improve humanity but created a monster.[76] This enduring theme illuminates the misgivings people may have about longevity enhancement.

Another common nature-based objection is that death is essential to life, and that by rejecting death, longevity enhancements would compromise human identity and dignity. Calling to question the certitude of death, the objection goes, would adulterate human nature physically and psychologically. A sense persists that our emotions, too—our capacity to be happy, excited, and aspirational, to feel a sense of urgency, and to cultivate loving relationships—will be rendered passionless if we go too far in a fight against aging.[77]

Fear of the Unknown

Ideological objections to longevity enhancement that are not grounded in religion or the sanctity of nature can all be tied to a fear of unknown consequences.

These fears of the unknown include:

- A prolonged period of disability and a sense that the world will turn into a "global nursing home"[78]
- Treatments may have unintended health consequences[79]
- Overpopulation will deplete natural and financial resources and cause high levels of poverty and hunger[80]
- Society won't be able to adjust to demands on key systems like retirement, the prison system, and international cooperation[81]
- A stagnation of cultural and intellectual evolution[82]
- Inequality and civil strife, which may take several forms:
  - An "enhanced" class that subjugates the "unenhanced" to political and social control, with an undertone akin to eugenics[83]
  - Exacerbating rich versus poor: the rich have access to life extension treatments, the poor do not, and sociopolitical divides become increasingly entrenched from one generation to the next, with a new twist of a biological aristocracy[84]
  - A struggle for job opportunities between older and younger generations due to a "glut of the able," that is, a ballooning of able-bodied workers that may distort supply and demand in the labor market[85]
  - Abuses of power wherein informed consent from treatment recipients is not adequately obtained[86]

IMPACT

Whether or not these ideological objections are credible, their persistence hinders research and development funding (especially from public sources), clinical trial participation, and adoption of interventions. As a result, it is difficult to achieve the virtuous cycle of adoption depicted in Figure 7 above, wherein:

1. Treatments are demonstrated as effacious and safe, leading to
2. Increase in demand for the treatments, followed by
3. Production increases accompanied by cost & price declines, finally resulting in
4. Increased accessibility.

These ideological objections also contribute to why "Americans are more worried than enthusiastic about using gene editing, brain chip implants and synthetic blood to change human capabilities."[87]

DIFFICULTIES

Believers arguing on the basis of religious scriptures and dogmas are unlikely to be dissuaded by arguments or data.

Some ideological aversion to human enhancement and radical life extension may be evolutionarily grounded in the sense that an intervention may be looked at—justifiably or not, consciously or not—as a type of contaminant.[88] That is, aversion to longevity treatments may be due to their association with a foreign agent that contaminates the body.

Social Perceptions of Aging and Biases Against Aging

SUMMARY

NEGATIVE PERCEPTIONS OF aging, or ageism, pervade societies and cultures. Such views associate aging with vulnerability, frailty, loneliness and decline. Most people assume they will one day be in a dramatically reduced state of health, and thus do not see the value of a much longer life. Ageism also affects many older adults' sense of career satisfaction and life-fulfillment through age-related biases in the workplace.

DESCRIPTION

Ageism is defined as the widespread prejudice, stereotyping, and discrimination against elders.[89] It is common across many societies and cultures. Prejudices and stereotypes related to aging include a lower quality of life, reduced productivity, loss of independence, and eventually becoming a burden to one's family and to society. The stereotypes and prejudices attached to aging can prevent even healthy older adults from finding work and contributing to society.

In the workplace, ageism can subject older individuals to unfavorable treatment from employers and coworkers who doubt their abilities to be productive contributors.[90] Despite these prejudices being unsubstantiated by research,[91] ageism at work generally begins at age 40[92] and is experienced by as many as two out of every three workers between the ages of 45 and 74.[93] Many studies provide evidence that older workers face discrimination in hiring and firing,[94] and have fewer opportunities for promotion, training, and interpersonal interactions at work.[95] Employers may perpetuate some of these biases by more readily laying off older workers because their salaries tend to be higher.

Despite numerous positive messaging campaigns, legal measures, and organizations to protect the growing aging population, evidence suggests that age stereotypes in the United States have worsened over time.[96] Globally, ageism has become more prevalent than racism or sexism.[97] Given the persistence of ageism across generations, societies and cultures, growing older and living longer remains unappealing to many without the promise of actually living better.

> "I am not surprised that people don't believe that we are actually very close to significantly extending human longevity. This is because Quacks and Charlatans have been discrediting the field of anti-aging for thousands of years. We have to find a way to get people's perception to be changed. I think that would change everything."
>
> **DR. BILL ANDREWS,**
> MOLECULAR BIOLOGIST AND GERONTOLOGIST

IMPACT

Social norms, misinformation, and a lack of information about aging perpetuate the confusion and distrust the general public harbors for longevity science and treatments.

While research and development in the field of aging has accelerated in recent years, the slow progress in preventing and curing aging-related diseases remains a significant deterrent to improving public perception. People understandably fear prolonged sickness and social isolation, and research shows that a majority of older adults would only consider life extension if it meant living in good health and with social independence.[98] This negative perception in turn limits scientific progress.

DIFFICULTIES

Like other forms of bias, ageist attitudes can be deeply embedded through cultural and evolutionary processes, making them difficult to surmount.[99] Although legislation against age discrimination has grown in recent years in many countries,[100] its effect on combating ageism in the workplace is inconclusive, and it is often difficult to prove that companies have engaged in ageism.[101]

Changing the archetypes related to aging and death and encouraging a new zeitgeist likely will require progress on several fronts. Demonstrating that an insidious decline in biological age need not be considered "natural," for instance, would help. Spreading the message that slowing down aging is the best way to keep people younger, healthier, more productive, and better-looking, might also favorably influence public opinion.

Layer 5: Natural Obstacles

No Set of Agreed-Upon Biomarkers for Quantifying Biological Age

SUMMARY

THERE IS CURRENTLY no one standard way for quantifying biological age. Without one consensus method, it will be difficult to assess the effectiveness of longevity treatments and to draw attention and funding to innovations that successfully slow, halt, or reverse aging.

DESCRIPTION

While one's "chronological age"—that is, the time elapsed since birth—is straightforward, individuals differ dramatically in how they exhibit the signs of aging and aging-related diseases. Some people, for example, suffer from debilitating aging-related diseases at the relatively early age of 60, while centenarians often remain in good health into their ninth decade and beyond. There is therefore a need to accurately measure one's "biological age"—the impact that the aging process has had on one's tissues, organs and cells.

To this end, the American Federation for Aging Research (AFAR) has established criteria for any biomarker that can be used to quantify biological age. Such a biomarker:

» "Must predict a person's physiological, cognitive, and physical function in an age-related way. In other words, it must predict the future onset of age-related conditions and diseases, and do so independently of chronological age.

» Must be testable and not harmful to test subjects. For example, it could be a blood test or an imaging technique. It must also be technically simple so that most clinical laboratories could perform the test accurately and reproducibly without the need for specialized equipment or techniques.

» Should work in laboratory animals as well as humans, since preliminary testing is always done in non-human subjects."

The AFAR list of criteria, in other words, requires measures of biological age to be simple and inexpensive to analyze, in a process that causes little or no discomfort. Finally, and perhaps most importantly, they must measure it accurately.[102]

Recently, Horvath and Raj have claimed that a collection of epigenetic clocks (i.e., DNA methylation-based biomarkers) satisfy these formerly elusive properties of molecular biomarkers of aging.[103] It remains to be seen, however, whether these claims will be accepted by the broader research community. Following the initial successes of epigenetic clocks, biomarkers of aging have again become a very active research area. Careful validation studies will be needed before epigenetic and other candidate biomarkers will be broadly accepted and used.

IMPACT

Biomarkers of aging are crucial for identifying and validating longevity interventions in humans. As long as there is no consensus biomarker or set of measures of biological age, it will be difficult to assess the effectiveness of longevity treatments. It will also be difficult to convince potential users of treatment efficacy, and to obtain funding for further research and innovation. Furthermore, clinical trials that use biomarkers have a higher success probability.[104]

DIFFICULTIES

The AFAR has described several difficulties with the identification of biological age measures. It is a challenge, for example, to separate the impact of aging-related diseases from that of the normal aging process, since both affect the body in ways that have an impact on the individual's lifespan. Furthermore, some of the physiological changes involved in biological aging cause harm to the body, while others do not—which makes it hard for the scientific community to determine which changes merit the most focus.

The need for additional biomarkers has been recognized by the U.S. National Institute on Aging, which has funded a major initiative on the "development of valid and reliable markers of aging-related biologic mechanisms for human studies."[105]

The Biological Indicators of Aging

ALTHOUGH WE ALL age differently, the aging process itself can be distilled into certain common denominators: categories into which the many different types of aging-related molecular and cellular damage can be grouped. Drawing mainly upon the most widely cited attempt of doing so, we outline and comment on ten "hallmarks of aging" below.[106]

Indicator 1: Genomic Instability

SUMMARY

CELLS ACCUMULATE GENETIC damage* to the nuclear DNA and mitochondrial DNA throughout the biological aging process. This genomic instability leads to an increased susceptibility to cancer in humans, as well as to stem cell exhaustion and cellular senescence (both of which are also hallmarks of aging). Genomic instability thus shortens human healthspan and lifespan. By minimizing aging-related genomic instability, the incidence of cancer, cardiovascular disease and cerebrovascular disease is likely to be significantly reduced.

DESCRIPTION

As the human body ages, genetic damage accumulates in its cells.[107] DNA incurs this damage from several sources, including replication errors, reactions with free radicals, infrared and ultraviolet radiation, and attacks from pathogens.[108] While DNA is constantly being repaired by various biological mechanisms, genetic damage nevertheless accumulates over time.

Several studies have shown that genetic damage can cause diseases and premature aging in humans.[109]

IMPACT

The full impact of genomic instability on the aging process is yet to be understood. Researchers have shown, however, that by minimizing DNA damage in mice, they can extend healthy lifespan and provide protection from the appearance of spontaneous tumors.[110] This suggests that genomic instability is associated with an increased susceptibility to cancer and a reduced lifespan.

DIFFICULTIES

No effective therapy has been found that can correct DNA damage in cells. While genetic engineering methods could conceivably be used for such a purpose, these are largely untested in humans and carry risks.

Indicator 2: Telomere Attrition

SUMMARY

TELOMERES ARE PROTECTIVE caps found at the ends of chromosomes. These caps shorten naturally as our DNA replicates, but this shortening is linked to the aging process and aging-related diseases. While short-lived species such as mice have considerably longer telomeres than longer-lived humans, research shows that re-elongation of telomeres can alleviate some symptoms of aging and extend lifespan. By negating detrimental telomere attrition, the incidence of cardiovascular, cerebrovascular, and autoimmune diseases is likely to be significantly reduced.

DESCRIPTION

Almost every type of human cell contains 46 chromosomes, each of which holds a vast amount of genetic information. Each chromosome is capped at either end by a telomere, a DNA-based structure that protects the vital genetic data within the chromosome from degradation during cell replication. With each such replication, however, the telomeres in each cell become shorter. When they get too short, the cell declines into replicative senescence (after a number of cell divisions known as the *Hayflick Limit*[111]), when it becomes incapable of replicating again—in other words, the cell becomes senescent. General DNA damage incurred at the telomere region can also cause cells to go into senescence mode even if the telomere has not become critically short.[112]

Telomeres are in turn protected by a complex of proteins called *shelterins*. When shelterins malfunction, it's been

*While "DNA damage" and "mutations" are often used interchangeably, they represent different types of deviations from the norm. A mutation is only a change in the genetic sequence of nucleotides. DNA damage, on the other hand, describes an abnormal change to the chemical structure of the DNA.

shown that the body undergoes accelerated aging and the aged tissues lose much of their regenerative capacity,[113] even if the telomeres remain at normal length. So the shelterins themselves may also be involved in the aging process.

A degree of telomere shortening is generally accepted as part of the normal aging process,[114] and is constantly held at bay in stem cells by *telomerase*—an enzyme that can re-elongate the telomeres and hold back the cells from the Hayflick Limit. Research suggests telomerase dysfunction may lead to accelerated aging and cancer.[115] Conversely, it has been shown that when telomerase is reactivated in aged telomerase-deficient mice, their accelerated aging process is reversed, leading to tissue repair and rejuvenation.[116]

IMPACT

The relationship between telomere length and longevity is still controversial, and there is some evidence that telomere *length* is merely positively correlated with health at old age, rather than causal.[117] There are also claims that the length of the telomeres is immaterial, whereas their *lengthening* is critical.[118] There is currently no consensus on the association between telomere length (or of its lengthening) and longevity.

DIFFICULTIES

The precise nature of the link between telomere length, attrition and aging is not yet clear. While there are solid theories regarding telomeres and aging, studies have shown that activation of telomerase, which re-elongates the telomeres, is also associated with increased risk for cancer.[119] Furthermore, while telomerase can be reactivated via genetic engineering,[120] any such treatments in human beings carry risks and require stringent ethical considerations.[121]

Indicator 3: Epigenetic Alterations

SUMMARY

BOTH GENETIC AND environmental factors change how genes are expressed—that is, how the instructions from certain DNA sequences are regulated and implemented. Researchers have extended the lifespan of flies and nematodes by preventing some of these epigenetic alterations. If we came to better understand the significance of these changes, and find a way to reverse them, such treatments would probably result in the mitigation of many aging-related conditions and diseases.

DESCRIPTION

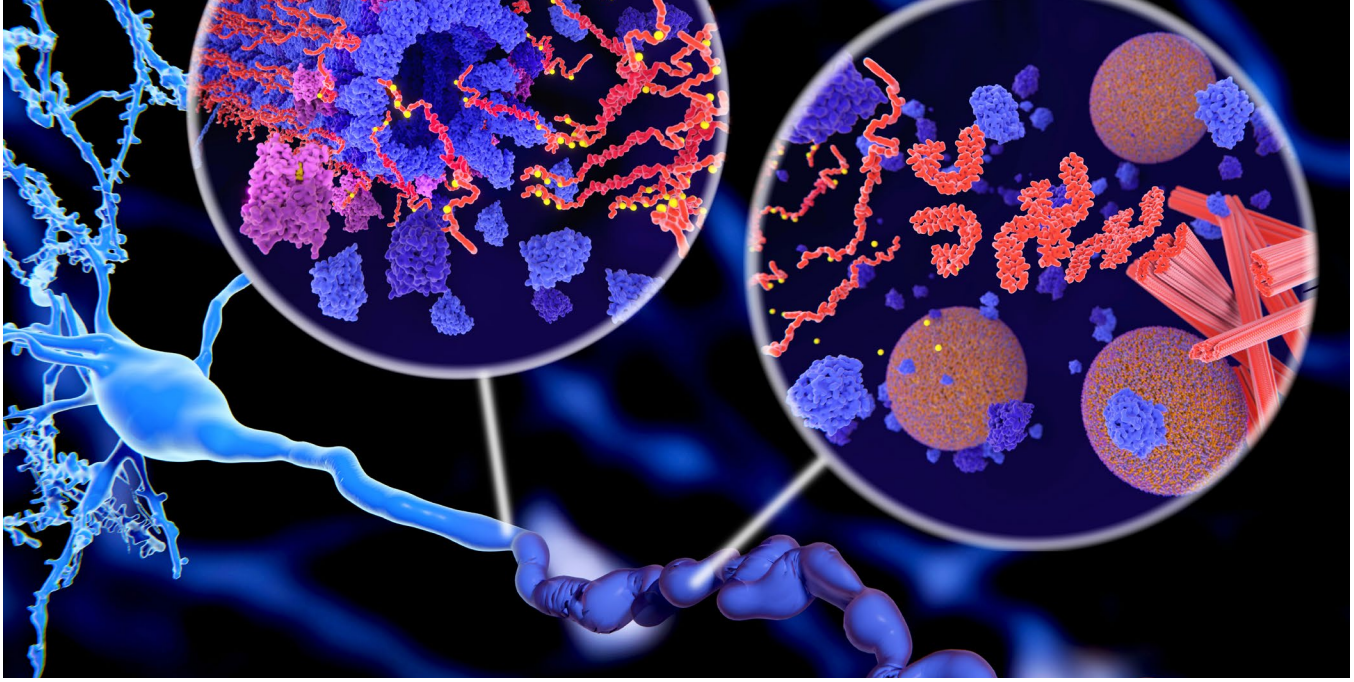
Epigenetics is the study of changes in gene expression that are not caused by changing the DNA sequence itself, but rather by alterations to proteins and the structure of DNA and RNA in the cell. The evidence supporting the hypothesis that some epigenetic changes are correlated with the symptoms of biological aging can be categorized into four groups:[122] enzymes of the sirtuin (Sir2) protein family;[123] DNA methylation;[124] alterations in the structure of chromosomes;[125] and a special class of microRNAs called gero-miRs.[126]

IMPACT

The extent to which epigenetic alterations contribute to the aging process and aging-related diseases and conditions remains unknown. Should it be discovered that epigenetic alterations are responsible for a significant part of the aging process, it may be relatively easy to counter them even with today's technology. Early experiments involving the mitigation of certain epigenetic alterations in mice have resulted in neuroprotective effects and prevented aging-associated memory loss.[127] In other experiments, epigenetic reprogramming extended lifespan in progeria mice and partially reversed the aging process in normal adult mice.[128]

DIFFICULTIES

Although efforts to develop therapeutics that work by manipulating certain epigenetic processes proceed, the precise way in which epigenetic alterations influence aging remains to be further elucidated.



Indicator 4: Loss of Proteostasis

SUMMARY

THE CELLULAR STATE of *proteostasis* describes the end-result of a complex array of mechanisms that regulate protein folding, function, and degradation. Faulty proteostasis is correlated with aging and aging-related diseases such as Alzheimer's, Parkinson's and heart failure. Proteostasis loss probably also accelerates senescence and drains the body's stem cell supply. Therefore, by minimizing aging-related loss of proteostasis, the incidence of cancer, cardiovascular disease and/or cerebrovascular disease may be significantly reduced.

DESCRIPTION

Proteostasis is the natural continual process of maintaining a high-quality protein workforce in cells.[129] The folding process of proteins often requires assistance from the surrounding internal cell environment, or from other proteins. Even after the proteins have been folded correctly, they are often stabilized by other molecules, called *chaperones*, which help to maintain their correct shape and function. Disruption of this process—loss of proteostasis—can result in aging and aging-related diseases.[130]

The production of some chaperones is impaired at old age,[131] and it is theorized that the decline in chaperone levels negatively impacts longevity. It's been shown that mice deficient in certain chaperones experience accelerated aging, while those that over-express certain chaperones live longer.[132]

The lifespans of several organisms—yeast, flies, nematodes, and mice—have been significantly extended by restoring proteostasis to normal levels.[133] Most notably, rapamycin has been used to restore proteostasis by preventing a decline of the protein-elimination system in cells, thereby delaying aging and extending lifespan in mice, yeast, nematodes and flies, even when administered late in life.[134] Spermidine—another restorer of proteostasis—has induced longevity in yeast, flies and nematodes as well.[135]

Impaired proteostasis is also at fault (at least partially) for some aging-related diseases like Alzheimer's (in which misfolded proteins aggregate in the brain) and Parkinson's.[136]

IMPACT

It is unclear just how much of an impact impaired proteostasis has on longevity, especially in humans. Rapamycin has extended mouse lifespan by 23-26%, but mice are very different from human beings. It's quite clear, however, that any plan to stop or reverse aging would have to address proteostasis.

DIFFICULTIES

Proteostasis is a general term for an enormously complex system containing tens of thousands of different proteins, all interacting with many others. Any tweaking of this system would probably lead to unexpected side effects.

Indicator 5: Deregulated Nutrient-Sensing

SUMMARY

THE BIOLOGICAL PATHWAYS that allow the body to sense and uptake nutrients become dysfunctional over time, leading to the development of aging-related conditions and diseases. Various manipulations of these pathways, however, have led to increased longevity in mouse models, and have reduced the incidence of cancer, cardiovascular disease and other aging-related diseases.

DESCRIPTION

Nutrients from food make their way to the bloodstream, where they should be absorbed by the cells in the tissues. Many cells, however, can only absorb the nutrients if they're aware of their presence. To that purpose, receptors on the cells' surface detect high concentrations of nutrients and "instruct" the cell to absorb them. These instructions pass into the cell via the nutrient-sensing pathways, leading to the desired result: uptaking nutrients and utilizing them for immediate energy gains, or as building blocks for more complex molecules. Impaired regulation of these pathways is associated with the emergence of aging conditions and diseases.[137]

An important nutrient-sensing pathway that changes with aging is the insulin and *IGF-1 signaling* (IIS) pathway, which is triggered by growth hormone (GH), insulin-like growth factor 1 (IGF-1) and insulin in response to high glucose concentrations in the blood. While the issue is still controversial, there is some evidence that impaired signaling via these pathways is positively associated with longevity in humans.[138] Additionally, caloric restriction, which affects the IIS pathway, improves health and increases lifespan in many species, including rhesus monkeys.[139]

Other enzymes involved in nutrient-sensing pathways that impact longevity include mTOR, AMPK and sirtuins. These enzymes are involved in pathways that allow the cells to sense and respond to high levels of amino acids in the blood, AMP* and NAD+**, respectively.[140] The sensing systems that rely on AMPK and sirtuins alert the cells when there is a scarcity of nutrients, and their upregulation—basically a signalling to the cells that there is not enough food around, thus triggering an emulated state of caloric restriction—leads to lifespan extension in mice.[141]

These lines of evidence clearly indicate that suboptimal regulation of nutrient-sensing reduces health and lifespan, and is thus an obvious obstacle that needs to be tackled.

IMPACT

How detrimental is the deregulation of nutrient-sensing pathways to human health and lifespan? The answer may come from a potential treatment for this obstacle, known as caloric restriction. In this treatment, which has a positive impact on both health and lifespan in many organisms, caloric intake is substantially reduced.

While caloric restriction has been shown to positively impact many different organisms, the most relevant ones for understanding its potential effects on human beings are rhesus monkeys. In these primates, a calorie-restricted diet has been shown to halve the rate at which aging-related conditions occurred, including sarcopenia, osteoporosis, arthritis, diverticulosis, cataracts and heart problems, as well as aging-related diseases like cancer and diabetes.[142] Partly as a result of these benefits, the rhesus monkeys also survived longer than their brethren usually do in captivity—the median survival rate in at least one experiment being the 90th percentile for the species.[143] In the most extreme case, one monkey reached the venerable age of 43—corresponding to 130 years in humans—even though the treatment began when he was at "late middle age."[144] These results, however, were not replicated in other studies in primates—though such studies on primates are relatively rare.[145]

Though more research is needed, it appears these benefits of caloric restriction could significantly prolong human healthspan, especially of obese individuals.

DIFFICULTIES

There is no dispute that obesity is a major risk factor for many chronic diseases. It remains to be seen, however, whether

* AMP (adenosine monophosphate) is a cousin of the energy-carrying molecule ATP (adenosine triphosphate). It is often used as a signal that indicates the cell is low on energy.

** NAD+ (Nicotinamide adenine dinucleotide) is electron-unladen form of the electron-carrying molecule NADH.

severe caloric restriction in non-obese humans has any benefit. Previous human studies led to inconclusive findings mainly due to low numbers of participants.

While caloric restriction might work well in non-obese human beings, it is accompanied by several risks and challenges. These are discussed in the next section on Remedies. A pharmacological manipulation of the nutrient-sensing pathways that does not induce the complex side effects of caloric restriction would provide a significantly improved solution—assuming, of course, that caloric restriction would indeed have a positive impact on non-obese humans.

Indicator 6: Mitochondrial Dysfunction

SUMMARY

THE MITOCHONDRIA PRODUCE most of the energy cells need to survive and prosper. Aging is known to be accompanied by mitochondrial dysfunction, which results in an elevated production of reactive oxygen species and decreased capacity for bioenergy generation. Mitochondrial dysfunction is thought to contribute to decline in cellular and organ function, exposing the aging person to aging-related diseases. By restoring mitochondrial balance, the incidence of sarcopenia, cancer, cardiovascular disease and cerebrovascular disease is likely to be significantly reduced.

DESCRIPTION

Mitochondria are small organelles residing in nearly every cell in the body and providing the cells with energy. The aging process is accompanied by mitochondrial dysfunction, which may contribute to the prevalence of aging-related diseases at old age.[146] The decline in mitochondrial function is apparent in several ways.

Mitochondrial mutations accumulate throughout the aging process. Mice with a large number of mitochondrial mutations have been shown to exhibit accelerated aging.*[147]

As mitochondria age, their bioenergy-generation capacity decreases, and they begin to generate a greater quantity of damaging byproducts known as reactive oxygen species (ROS). These byproducts are suspected of accelerating the rate of muscle loss experienced in aging (also known as sarcopenia)[148]. At high levels, ROS damage the cell and may lead to senescence.[149] Additionally, aging mitochondria accumulate damage to their DNA, leading to malfunctioning mitochondria that produce less energy but may be resistant to breakdown.

IMPACT

It needs to be further researched to what extent mitochondrial dysfunction affects the organism as a whole, instead of just the cells. There is evidence that endurance training can improve mitochondrial function and proliferation, which in turn is associated with the prevention of premature mortality and protection from old-age conditions in mice.[150] If similar treatments were available to the general public, and if the same biological mechanisms were to apply for human beings, then improvement of mitochondrial function would help to alleviate and postpone many old-age conditions.

DIFFICULTIES

The main difficulty in dealing with mitochondrial dysfunction seems to be that our understanding of this obstacle needs to be further expanded. More research is required to better understand the causal and associative links between mitochondria and the aging process.

*It is still highly controversial, however, whether mitochondrial mutations increase people's susceptibility to aging-related diseases and conditions

Indicator 7: Cellular Senescence

SUMMARY

SENESCENT CELLS—"OLD" CELLS that no longer divide or grow as they should—accumulate in the body's tissues during the aging process. They may contribute to the emergence of aging-related diseases and conditions, possibly by releasing chemical signals that induce inflamm-aging—a constant state of inflammation. Elimination of senescent cells is therefore expected to reduce the incidence of cancer (since it would lead to a reduced inflammatory, pro-tumor environment), cardiovascular disease and cerebrovascular disease. It would probably also reduce the susceptibility of old people to infectious diseases.

DESCRIPTION

Cells that reach a state of senescence stop dividing, growing and functioning as they should. Cells may senesce due to telomere attrition and/or DNA damage, which lead to the cell's final decision to go into senescent mode in an attempt to avoid the possibility that it might become a cancer cell.[151]

Senescent cells can accumulate in the body, especially in the liver, skin, lung and spleen—but not in the heart, skeletal muscles, or kidneys.[152] The number of senescent cells in the tissues more than doubles as people age, and they are known to release chemical messages that encourage inflamm-aging—a state of whole-body inflammation that is thought to promote aging and its related conditions and diseases.[153]

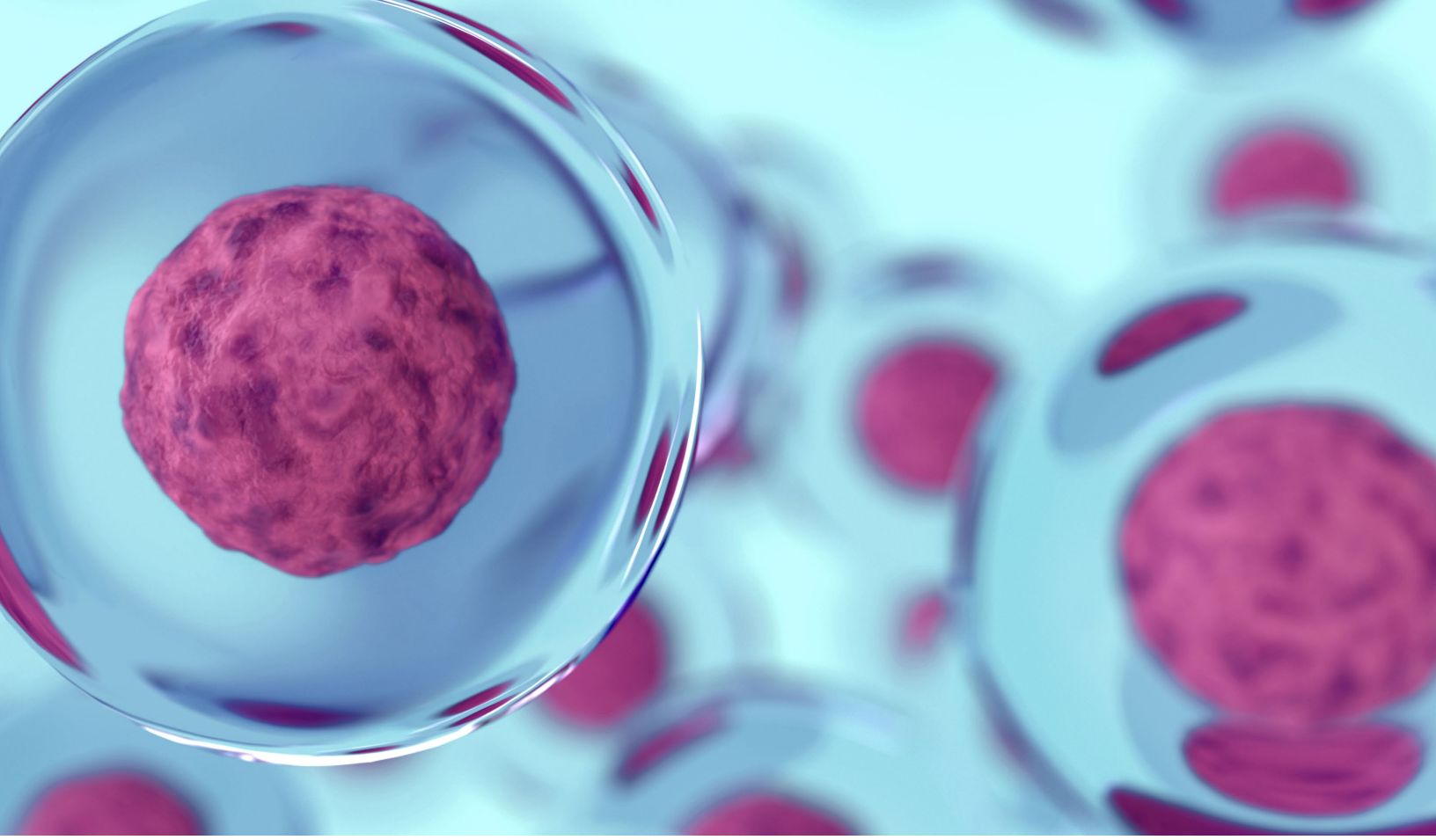
Nonetheless, there is still some controversy whether cellular senescence indeed causes biological aging, and whether elimination of senescent cells would extend longevity. Evidence is mixed. It is possible that senescent cells exhibit a "Goldilocks" property, wherein the body uses cellular senescence to protect itself from cells that pose cancerous threats, but when too many cells become senescent they cause damage to the body.

IMPACT

It has become clear that the accumulation of senescent cells plays an important role in the aging process. In mice, senescent cell accumulation impairs physical functions such as walking speed and daily activities, and reduces muscle strength and body weight.[154] It seems likely that senescent cells have a similar effect in humans as well.

DIFFICULTIES

The main difficulty for finding remedies to this obstacle is that the science behind cellular senescence is not yet completely understood. The link between cellular senescence and aging needs to be further researched.



Indicator 8: Stem Cell Exhaustion

SUMMARY

THE REGENERATIVE CAPACITY of tissues declines as they age, leading to a variety of aging-related conditions. This decline is thought to be caused by the depletion of stem cells that are supposed to replenish and maintain the cells in those tissues. Stem cell exhaustion, therefore, is a major obstacle on the path towards extended healthspan and lifespan.

DESCRIPTION

The regenerative capacity of tissues declines as they age, leading to a variety of aging-related conditions. This decline is thought to be caused by the depletion or dysregulation of stem cells that are supposed to replenish the cells in those tissues. Stem cell exhaustion, therefore, is a major obstacle for extending healthspan and lifespan.[155]

Experiments have shown that stem cell transplantation from young to old mice extends lifespan and restores tissues' regenerative capabilities,[156] strongly suggesting that stem cell exhaustion plays an important causative role in the aging process.

IMPACT

Stem cell exhaustion can reduce the efficiency of the immune system, and lead to muscle loss, a decline in bone mass and slow wound healing.[157] A solution to this obstacle, therefore, could significantly extend healthspan.

DIFFICULTIES

Enhancing the activity of stem cells can lead to unwanted side effects, as the stem cells can senesce at an accelerated rate, resulting in premature aging.[158] Slowing their activity, on the other hand, can cause premature aging as well. There's a clear need, therefore, for finding the "sweet spot" for stem cell activity and guiding the cells in that direction. We also need further development of effective tools to operate on stem cells in the tissues and either replace or rejuvenate them.

Indicator 9: Altered Intercellular Communication and Inflamm-aging

SUMMARY

AGING IMPACTS HOW cells communicate with each other, which can cause inflamm-aging: a constant state of low-level body-wide inflammation, which in turn brings about several aging-related conditions. Countering inflamm-aging would improve the immune system's activity and could mitigate many aging-related conditions.

DESCRIPTION

Cells communicate with each other by sending chemical signals of various kinds. This ability explains why aging can be a "contagious" process, for example how senescent cells can urge other cells—even in other tissues—to undergo senescence themselves.[159]

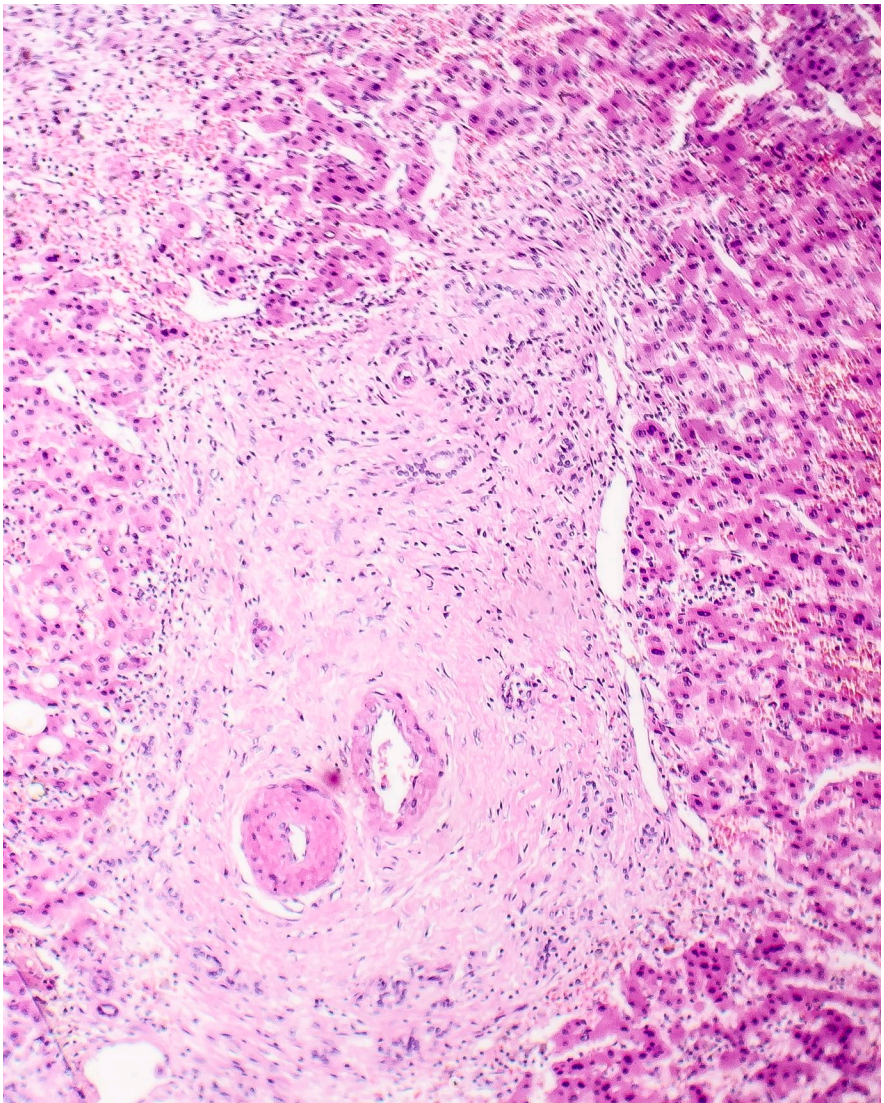
Senescent cells release proinflammatory molecules that contribute to a general state of inflammation in the body. This condition is associated with aging and many aging-related diseases including Alzheimer's,[160] atherosclerosis,[161] Type II diabetes,[162] and cancer,[163] and can hinder the function of adult stem cells.[164] Constant inflammation can even accelerate telomere attrition, which then promotes cellular senescence.[165]

IMPACT

The inflamm-aging hypothesis is still a relatively new one, and there is no guessing its impact on longevity and the human lifespan. There is compelling evidence, however, that it is a major contributor to aging and aging-related conditions and diseases.

DIFFICULTIES

In addition to needing more scientific study, it's now clear that inflamm-aging is a complex process related to numerous tissues simultaneously secreting varied chemical signs. Fine-tuning this process via a single treatment seems nearly impossible, and would probably require lifelong administration.



Indicator 10: Changes in the Extracellular Matrix

SUMMARY

THE COMPOSITION OF the extracellular matrix changes throughout the aging process. Long-living molecules in the matrix can degrade or undergo various modifications, which can lead to loss of tissue function and promote the emergence of aging-related diseases and conditions.

DESCRIPTION

Every cell in the human body resides within the extracellular matrix (ECM): a network of macro-molecules, secreted by the cells themselves. The ECM accounts for most of the body's mass, and can undergo changes through the aging process. These changes include glycation, oxidation, carbamylation, carbonylation, and succination. In this section we focus on the example of ECM glycation.

During the aging process, the molecules that make up the ECM may undergo a process of cross-linking. This begins with the bonding of amino acids in the ECM to abundant circulating molecules, especially glucose. The resulting structures then sometimes rearrange and bond to other, nearby proteins in the ECM. Such links are called Advanced Glycation End-products (AGEs).[166] An accumulation of AGEs in the extracellular matrix is suspected of increasing the stiffness of body tissues—usually tendons and muscles—often with catastrophic consequences.[167]

IMPACT

There are several consequences to the aging-related accumulation of AGEs and cross-linked ECM proteins and molecules. For example:

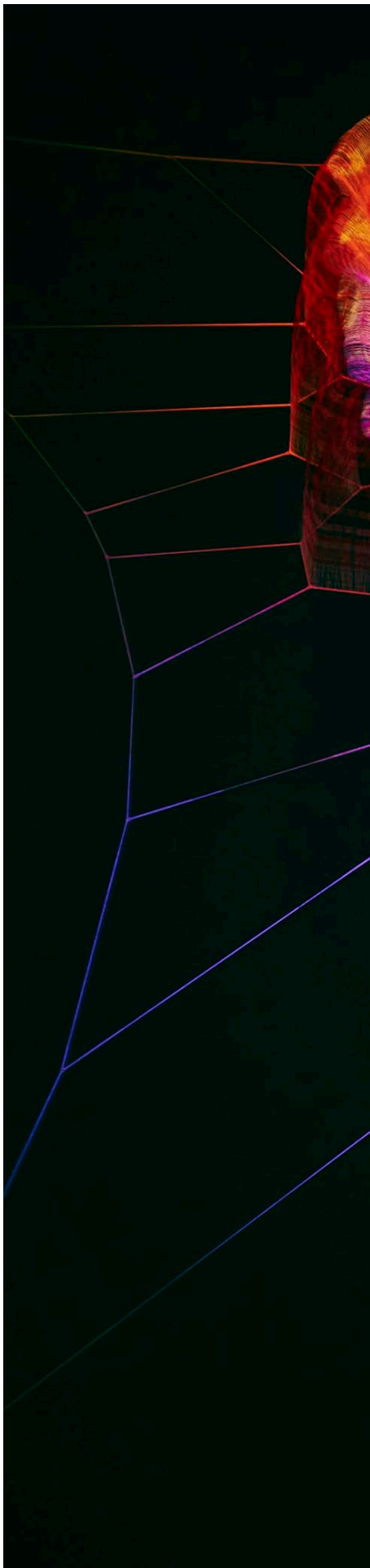
- AGE accumulation can inhibit wound repair and promote inflammation responses.[168]
- AGE accumulation makes certain tissues—like tendons—more fragile, which can impair their function.[169]
- AGE accumulation reduces the cells' capability to replenish and rejuvenate the ECM.[170]
- Cataracts are thought to be the result of the aggregation of proteins that cause the eye lens to become opaque.[171] [172]
- Skin aging is partly caused by the progressive cross-linking of ECM molecules.[173]
- Arterial stiffening is largely caused by cross-linking of ECM molecules,[174] and is thought to contribute to the emergence of cardiovascular diseases.[175]
- ECM stiffening, which results from the cross-linking of ECM molecules, is correlated with a decrease in muscle strength[176] and an increase in muscle stiffness.[177]

DIFFICULTIES

The precise mechanism by which changes to the ECM bring about aging-related diseases and conditions is still unclear. More sophisticated research tools to observe ECM changes are required for a better understanding of its role in the aging process. Furthermore, as the ECM's composition changes from one tissue to another, it is difficult to devise one silver bullet solution to aging-related changes in the ECM.

Conclusion

This concludes our analysis of the most relevant obstacles to hastening a preferred future of longevity. In the next section, we examine some of the most prevalent emerging and ongoing countermeasures to these obstacles, which we call Remedies.



04.

REMEDIES FOR THE OBSTACLES

04

Introduction

OBSTACLES, AS DEFINED in this report, represent emerging and ongoing issues that hinder the fulfillment of the preferred future of longevity. Human ingenuity ensures that for each obstacle, countermeasures—which we call remedies—are being developed to overcome its negative impact. In this section, we conduct a landscape analysis in which we (a) review the most prevalent remedies used today, (b) identify their current status and importance, and (c) analyze the challenges to using and implementing them.

> "If you're not thinking about aging, you're never going to contribute anything to the solution. Or if you think aging is hopeless, you're never going to contribute anything to the solution."
>
> **DR. GREG FAHY,** CRYOBIOLOGIST

WANT TO JUMP STRAIGHT TO THE BREAKTHROUGH SOLUTIONS? TURN TO PAGE 200 TO EXPLORE THE GAME-CHANGERS WE'VE IDENTIFIED THAT COULD SIGNIFICANTLY ACCELERATE THE FIELD OF LONGEVITY.

Definitions and Methodology

We now focus on countermeasures, or remedies, to the obstacles reviewed in the previous section. This analysis is not exhaustive. Rather, our goal is to analyze the most influential and promising emerging and existing remedies in the field of longevity and life extension today.

This section does not deal with potential future remedies—those are covered in Section 6, Breakthroughs. In Section 5 we will synthesize the insights related to both the obstacles and remedies into the grand challenges of longevity.

We separate the remedies into two distinct categories:

» **Nature-based remedies** relate to the human body, or have a direct effect on it. These include remedies like genetic engineering, tissue replacement, or dietary supplementation.

» **Societal remedies** focus on the social, regulatory and legal sectors, such as retirement reform or utilizing AI to accelerate drug development.

In both categories, the remedies are ordered according to the number of obstacles they help to directly address. **The order does not imply an assessment of the relative impact of the remedies**. Some remedies, for example, may affect just a couple of obstacles, but by addressing said obstacles they could catalyze a cascade of downstream benefits. We leave it to the reader's intuition and imagination to assess the relative impact of the various remedies.

The remedies analyzed in this section are by no means exhaustive. Indeed, there are bound to be many remedies that are not covered in this section, but have clear potential to postpone the emergence of aging-related diseases and conditions. These include repurposing drugs, as well as mitochondrial, transcriptomic, proteostasis, lysosomal and telomere therapies, among others. We encourage readers to seek out more information on these and other potential remedies in addition to those included here.

The remedies we've analyzed are summarized in Figure 4.1.

FIGURE 4.1. REMEDIES

CATEGORY	REMEDY	NUMBER OF OBSTACLES DIRECTLY ADDRESSED
Nature-Based Remedies	Identifying Promising Biomarkers for Quantifying Biological Age	12
	Genetic Engineering of the Human Body	11
	Epigenetic Reprogramming	11
	Cell and Tissue Replacement Therapies	10
	Lifestyle Interventions	8
	Hormesis-Promoting Therapies	6
	Supplementation with Biomolecules	4
	Quantified-Self Apps, Wearables, Embeddables and Ingestibles	4
	Blood-Based Treatments	4
	Minerals Supplementation	4
	Dietary Restriction and Intermittent Fasting	4
	Senolytic and Senomorphic Therapies	3
	Thymic Rejuvenation	3
	Human Epigenomics Mapping	2
	Cognitive Enhancement for Improving Performance	2
	Data Collection on Centenarians and Supercentenarians	1
Societal Remedies	Longevity and Life Extension Movements and Campaigns	7
	Improving Science and Media Literacy	5
	Reclassifying Aging Processes and Symptoms as a Treatable Condition	4
	DIY-Medicine	4
	Artificial Intelligence for Drug Development	4
	Promoting and Embracing a Multi-Stage Life	4
	Retirement Reform	3
	Governments Promote Generic Drugs	3
	Regulations to Facilitate Competition in the Pharmaceutical Market	3
	Universal Adherence to Common Data Standards	3
	Regulations to Expedite Clinical Trial Process	2

Identifying Promising Biomarkers for Quantifying Biological Age

RELEVANT OBSTACLES

- Slow Pace of Drug Development and Approval
- No Set of Agreed-Upon Biomarkers for Quantifying Biological Aging
- Genomic Instability
- Telomere Attrition
- Epigenetic Alterations
- Loss of Proteostasis
- Deregulated Nutrient-Sensing
- Mitochondrial Dysfunction
- Cellular Senescence
- Stem Cell Exhaustion
- Altered Intercellular Communication and Inflamm-aging
- Changes in the Extracellular Matrix

SUMMARY

Aging biomarkers can indicate a person's biological age (a term which largely refers to the accumulation of damage in the body, caused in the course of the aging process), and reflect any changes to it following longevity treatments. Without aging biomarkers, researchers cannot assess the efficacy of proposed treatments, and governmental authorities have a more difficult time evaluating and potentially approving such treatments.

DESCRIPTION

Aging biomarkers are tools that can help us estimate an individual's biological age, and assess his or her expected healthspan and lifespan.[178] According to the American Federation for Aging Research, the ideal aging biomarker would determine a person's physiological, cognitive, and physical function, predict the time before onset of aging-related conditions and diseases for individuals regardless of their chronological age, and would be easily and repeatedly testable.[179] It does not seem likely that a single indicator will be able to do all that, and thus the focus today is on discovering sets of biomarkers that together can fit the demands.

IMPORTANCE FOR OVERCOMING OBSTACLES

There is an urgent need for a set of aging biomarkers that the pharma industry, academic researchers and government can accept. Without such biomarkers, it's extremely difficult to assess the efficacy of anti-aging treatments, or decide when such treatments should be administered.

CURRENT STATUS AND USES

The types of aging biomarkers that are currently being researched, according to Xia and colleagues, are summarized below in Figure 4.2.[180]

New methods for assessing aging are constantly being developed. Several groups research "composite biomarkers" based on multiple biomarkers. Artificial intelligence is also being used in this field, as a way to uncover subtle aging-related changes. In a 2016 research project, 21 deep neural networks were employed to uncover correlations between several markers examined in 60,000 blood samples, and the chronological age of the sample provider.[181] AI engines have also been used to assess a person's age according to his or her external features (e.g., facial photo) and blood test results.[182]

CHALLENGES

The utility of clinical biomarkers is beyond debate, but the same cannot be said about molecular biomarkers. While thousands of scientific articles have been written on molecular biomarkers of aging, there is controversy as to the validity of claims surrounding accuracy and predictive utility. As a result, there is a general confusion in the biomedical research community on suitable molecular biomarkers of aging.

Given the complexity of the aging process, even the most promising aging biomarkers may not be sufficient for quantifying it. There is need for better validation of aging biomarkers, as well as for achieving a better understanding of their capabilities and limitations.

EPIGENETIC BIOMARKERS: A NEW HOPE?

Epigenetic biomarkers based on chemical modifications of the DNA known as methylation ("epigenetic aging clocks") are the current benchmark for molecular biomarkers of aging. Epigenetic clocks have been carefully validated by many research groups in dozens of epidemiological cohort studies,[183] which helps to explain why a recent review of candidate biomarkers concluded that epigenetic clocks constitute the most promising biomarkers of aging.[184]

Early versions of epigenetic clocks focused on measuring chronological age in all tissues. Newer epigenetic clocks (e.g., DNA methylation GrimAge) are designed to predict lifespan and healthspan. The predictive utility of DNAm GrimAge has been validated in large cohorts and large sample sizes.[185] DNA methylation measurements are considered remarkably robust[186] and are already being used in human clinical trials of anti-aging interventions.

Yet while standard clinical and DNA methylation-based biomarkers are arguably necessary for future clinical trials, they may not be sufficient. It will be important to develop, and carefully validate, additional biomarkers of aging. The need for additional biomarkers has been recognized by the U.S. National Institute on Aging, which has funded a major ongoing initiative on the "development of valid and reliable markers of aging-related biologic mechanisms for human studies."[187]

FIGURE 4.2. BIOMARKERS OF AGING UNDER RESEARCH

Molecular Biomarkers *(Note that the biomarkers in this list are still being researched to assess their efficacy)*	
CATEGORY	**BIOMARKERS**
DNA and Chromosomes	Telomere length
	DNA damage, as quantified by immunohistochemistry of γ-H2A.X. Other markers of DNA damage include CRAMP, EF-1a, stathmin, N-acetyl-glucosaminidase, and chitinase
	Epigenetic modifications, H3K9me3, Heterochromatin Protein 1, methylation profiles, such as Horvath's epigenetic clock or the lifespan predictor DNA methylation GrimAge
RNA and Transcriptome	Transcriptome profiles, especially the transcription signatures of genes with an age-dependent expression profile
	Non-coding RNAs, especially MicroRNAs with an age-dependent expression profile, like miR-34a, miR-151a-3p, miR-181a-5p, and miR-1248
Metabolism	Nutrient sensing, as indicated by the levels and activity of members of nutrient sensing pathways, like IGF-1 and mTOR, AMPK and sirtuins
	Protein metabolism, as indicated by the accumulation of advanced glycation end products (AGEs)
	Lipid metabolism, as indicated by triglyceride, phospholipid and sphingolipid levels
Oxidative Stress and Mitochondria	Levels of oxidative stress, as measured by the levels of biological components like o-tyrosine, 3-chlorotyrosine, 8-iso prostaglandin F 2a, 8-hydroxy-2-deoxyguanosine, 8-hydroxyguanosine and 3-nitrotyrosine, which are the products of oxidative damage
	Mitochondrial dysfunction can be assessed via respirometric profiling of muscles, ATP levels, mitochondrial ROS production, mitochondrial potential, SOD2 levels, or by common phenotypes, like walking speed; grip strength may also be an indicator of mitochondrial dysfunction
Cell Senescence	Senescence-associated β-galactosidase indicates increased lysosomal mass; p16 INK4A is evident in cells that have gone into a complete cell cycle arrest; activated and persistent DNA-damage response can also reveal the presence of senescent cells, as can the more general senescence-associated secretory phenotype (SASP)
Inflammation and Intercellular Communication	Interleukin-6, tumor necrosis factor-alpha, monocyte chemoattractant protein-1, matrix metalloproteinases, and other proteins associated with SASP
Proteostasis	Autophagosome formation, proteosomal activity, rate of elimination of protein aggregates, chaperone activity

Phenotypic Biomarkers	
Physiological Function	Walking speed, chair stand test, standing balance, grip strength, and muscle mass
Standard Clinical Biomarkers	Blood pressure, glucose measurements, C-reactive protein, blood cell counts
External Human Features	Facial features

Source: Xia et al., Molecular and Phenotypic Biomarkers of Aging (2017)

Genetic Engineering of the Human Body

RELEVANT OBSTACLES

» Accessibility of Treatments

» Genomic Instability

» Telomere Attrition

» Epigenetic Alterations

» Loss of Proteostasis

» Deregulated Nutrient-Sensing

» Mitochondrial Dysfunction

» Cellular Senescence

» Stem Cell Exhaustion

» Altered Intercellular Communication and Inflamm-aging

» Changes in the Extracellular Matrix

SUMMARY

Genetic engineering techniques can be used to mitigate many of the indicators of aging. They could also help ensure the accessibility of treatments, since (unlike some epigenetic alteration treatments, and practically all drugs) they may only need to be administered once.

DESCRIPTION

Genetic engineering can be used to reprogram cells inside the human body in a way that alleviates and postpones aging-related conditions and diseases.

While genetic engineering has received harsh criticism in the past because of its many risks and unintended consequences (like causing cancer[188]), new methods like CRISPR-Cas9 gene editing are supposedly safer and more precise. [189] While such claims are still disputed,[190] several other CRISPR-based variations of genetic engineering are currently being developed. Some have demonstrated better safety than the original CRISPR method.[191]

There is clear consensus that the genetic engineering tools we have today are far more powerful, efficient and cheap than ever before, allowing genetic engineers to conduct feats that once would have been considered impossible.[192] New techniques for genetic engineering are already being developed and tested for treating various diseases like cancer, muscular dystrophy, blood disorders, AIDS, Huntington's disease, and others.[193]

IMPORTANCE FOR OVERCOMING OBSTACLES

Genetic engineering of cells in the human body could be used to:

» Activate telomerase, which could counter telomere attrition. When telomerase was reactivated via genetic engineering in aged mice, aging-related tissue degeneration was reversed.[194]

» Alter enzymes that are involved cellular epigenetics, in a way that extends longevity.[195]

» Reduce the incidence of genomic instability events, or mitigate their negative impact (possibly by forcing the unstable cells to self-destruct). Mice genetically engineered to receive better protection from genomic destabilizing events have exhibited extended healthy lifespan.[196]

» Alter the function of mitochondria to bring about a beneficial state of mitohormesis. Mice that were genetically engineered to achieve this exhibited extended lifespan and slower aging.[197]

» Restore proteostasis. Genetically engineered mice with improved proteostasis exhibited a delayed aging process.[198]

» Prevent cells from senescing, or enforce apoptosis (i.e., controlled cell death) instead of senescence. Genetic engineering that induced apoptosis in senescent cells in vivo extended lifespan in mice and in flies, delayed the emergence of tumors, and mitigated aging-related negative effects in the body's tissues.[199]

» Rejuvenate stem cells or mitigate inflamm-aging.

It's important to note that in many of the above use cases, the individually affected animals were not directly genetically engineered but rather were transgenic—meaning they contained DNA from another organism. Transgenic mice are not necessarily created via genetic engineering on adult organisms, but rather by engineering the single cell—the fertilized egg—from which a mouse will develop. These mice are later bred with other transgenic mice, creating a progeny of more transgenic mice. While such methods cannot practicably be used to genetically engineer human adults, it is highly likely that as the science of genetic engineering develops, scientists will be able to genetically engineer cells and even entire tissues in the bodies of human adults as well.

Genetic engineering may also provide a way to ensure long-term accessibility to treatments. Costly drugs will no longer need to be manufactured in factories and sold to patients throughout their lives, but could instead be manufactured in the patient's body itself with one single treatment.[200]

CURRENT STATUS AND USES

Genetic engineering applications in human beings are still in testing phases, largely due to fear of unexpected complications arising from the treatments. However, maverick scientists and DIY enthusiasts are already starting to conduct genetic engineering experiments on themselves and on consenting patients.[201] In one extreme case in China, a researcher genetically engineered three human embryos (two of which were born in 2018), hoping to provide them protection from potential future HIV infection.[202] Despite many unaddressed safety and ethical concerns, it is possible that the floodgates for conducting genetic engineering in human beings have already opened.

CHALLENGES

There are several challenges that obstruct the path of genetic engineering overcoming obstacles to longevity.

For one, the basic mechanisms of aging are not yet well understood, so any attempt to genetically engineer the human body to correct these mechanisms may have detrimental effects. Moreover, even state-of-the-art genetic engineering techniques still contain undeniable risk of causing harmful mutations (which can result in cancer and other diseases), which must be taken into account when considering whether to utilize them for treating aging. Of special concern is the transgenerational effect: a single treatment could alter both the recipient's genetics as well as the genetics his or her future children. Many are concerned that future children will essentially be engineered without being able to choose how or why.

Testing new therapies in consenting palliative, terminal patients, or as a last result for old people suffering from a late-stage aging-related disease, could accelerate the development of new cures.

Opposition to genetic engineering in humans is often driven by ideological and religious beliefs, which may cite the natural wholeness of the human body and the fear of creating different biological classes. The ethics of genetic engineering in humans are not clear yet, but ethical concerns may minimize the use of this remedy. Additionally, there is widespread concern about genetically-modified organisms, and it is likely that this fear is relevant for the public approval of any attempt to genetically engineer human beings.

Epigenetic Reprogramming

RELEVANT OBSTACLES

- Accessibility of Treatments
- Genomic Instability
- Telomere Attrition
- Epigenetic Alterations
- Loss of Proteostasis
- Deregulated Nutrient-Sensing
- Mitochondrial Dysfunction
- Cellular Senescence
- Stem Cell Exhaustion
- Altered Intercellular Communication and Inflamm-aging
- Changes in the Extracellular Matrix

SUMMARY

Epigenetic reprogramming treatments make changes to the epigenome—the intricate molecular machinery that regulates gene expression. These treatments have the potential of being safer and more transient than genetic engineering, but may be just as powerful.

DESCRIPTION

While genetic engineering is focused on making changes to the genetic code, epigenetic reprogramming is all about controlling which genes are expressed, and at what times ("gene expression" refers to the process by which information encoded in one's genes is manifested into an observable phenotype). Regulation of gene expression is usually achieved by controlling the structure of the DNA strands so as to open or close certain genes for transcription, the first step of gene expression.[203]

Epigenetic reprogramming can be achieved by technologies similar to those used for genetic engineering purposes, such as zinc fingers, transcription activator-like effectors, and CRISPR/Cas9 modules.[204] The modules used in these techniques target specific parts of the genome, which are then "shut down" or "opened up" so that the genes in those parts are switched off or expressed. There are also transcriptomic drugs that rely on epigenetic mechanisms, like RNA interference and antisense therapies.

Epigenetic reprogramming has been used in various ways to counter aging-related conditions, including the reactivation of telomerase, which prevents telomere attrition in cells,[205] and the reversal of gene-silencing patterns that are associated with aging, restoring them to a youthful state.[206]

IMPORTANCE FOR OVERCOMING OBSTACLES

High-level epigenetic reprogramming has the potential to prevent or cure many aging-related diseases and conditions like cancer, inflammaging, sarcopenia, cardiovascular and cerebrovascular diseases. Unlike genetic engineering, epigenetic reprogramming is generally reversible,[207] and carries less risk than genetic engineering for the changes to be passed on to the next generation.[208]

Certain methods of epigenetic reprogramming can completely reset one's epigenetic clock to a prenatal state.[209] These and other insights have led to a new age-reversal strategy: turning back cells' biological clock without affecting cellular identity.[210 211 212 213 214]

CURRENT STATUS AND USES

The field of epigenetic drugs and treatments is on the rise. According to the Human Epigenetic Drug Database, there are currently eight epigenetic drugs that have been fully approved by the FDA. Hundreds more are currently in various phases of clinical trials.[215] Some, like sirtuin-inducing compounds, are being tested for aging-related diseases and conditions such as "chronic subclinical inflammation". Overall, epigenetic drugs and treatments are recognized as being a novel and intriguing strategy that can help fight aging.[216]

CHALLENGES

There is still much unknown about the human epigenome, especially in relation to its different manifestations in different tissues and cells in the body. Due to our limited understanding of the human epigenome, interventions or manipulations of components in the system can have unintended consequences. While epigenetic changes are less likely than genetic changes to have a transgenerational effect, there is still risk of transmitting some epigenetic changes to the next generation. Finally, epigenetic reprogramming strategies could increase the risk of malignant transformation, i.e., cancer.

> "If aging is caused by inappropriate gene action, and we have technology to go in and control gene action, suddenly the picture changes."
>
> **DR. GREG FAHY,** CRYOBIOLOGIST

Cell and Tissue Replacement Therapies

RELEVANT OBSTACLES

- Genomic Instability
- Telomere Attrition
- Epigenetic Alterations
- Loss of Proteostasis
- Deregulated Nutrient-Sensing
- Mitochondrial Dysfunction
- Cellular Senescence
- Stem Cell Exhaustion
- Altered Intercellular Communication and Inflamm-aging
- Changes in the Extracellular Matrix

SUMMARY

Cell and tissue replacement therapies have the potential to replace aged cells, tissues and even entire organs with young ones.

DESCRIPTION

Cell and tissue replacement therapies, including stem cell therapies, can be used to replace aging and dysfunctional cells and tissues with young and highly-functional ones. The transplanted components can be sourced from young donors, from cells and tissues grown in the lab, or from synthetic biocompatible materials.

IMPORTANCE FOR OVERCOMING OBSTACLES

As cells and tissues grow older and incur damage, an appealing option would be to simply replace them with younger cells and tissues. Cell and tissue replacement should enable that in the future, and thus help deal with many of the cellular changes that accompany aging. It could also help cure many aging-related diseases, including Alzheimer's, Parkinson's, or cardiovascular and cerebrovascular disorders, by replacing the damaged cells and tissues with healthy ones.

CURRENT STATUS AND USES

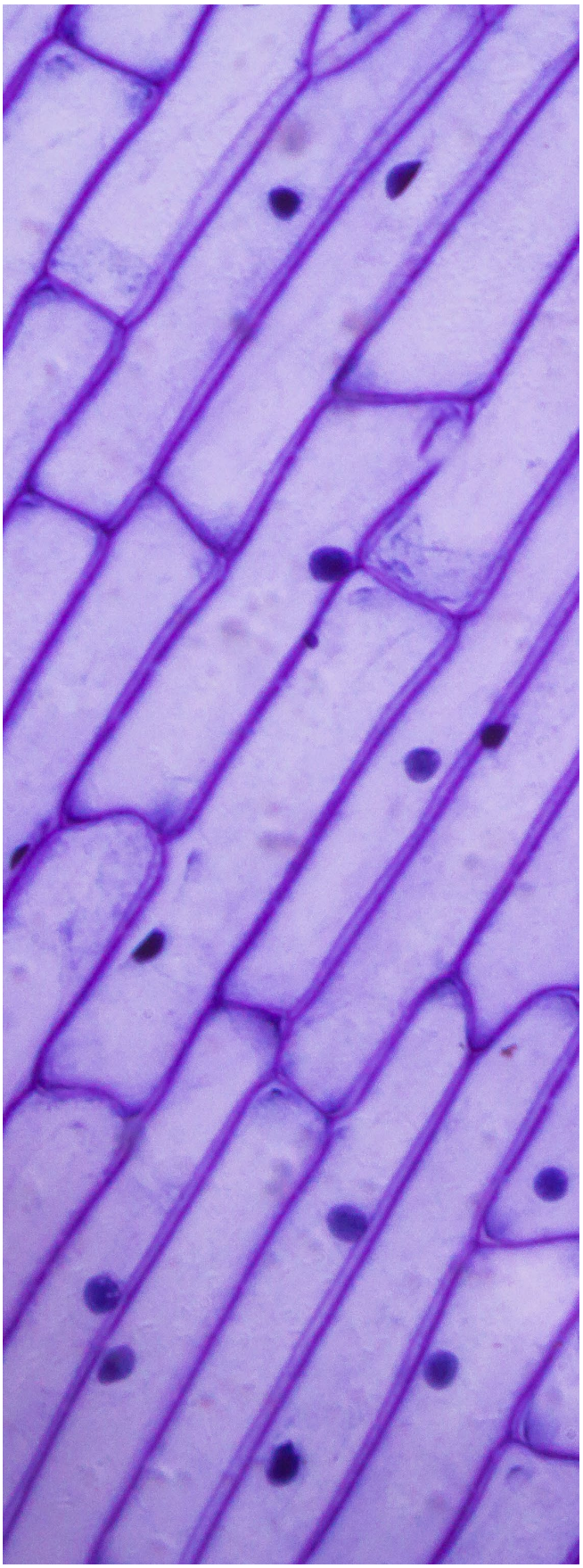
So far, the only kind of transplantation that has demonstrated an effect on aging itself is stem cell transplantation. Pluripotent stem cells have an advantage over other cells, since they can proliferate endlessly and bring forth young and needed cell progeny to fill the niche for which they were implanted. Stem cells from young cells have been transplanted into old mice to successfully extend their lifespan.[217] Stem cell transplantation also has the potential to treat several aging-related diseases like Alzheimer's (a treatment which is now available in Japan),[218] cardiovascular diseases,[219] Parkinson's and others.[220]

Other kinds of transplantations can help mitigate the effects of aging-related diseases,[221] and can be supported by exponential technologies. 3D printers, for example, have been used to print titanium hips for more than 100,000 patients, most of them elderly, who needed hip replacements.[222] Heart transplants have been used widely to replace damaged hearts.[223] Pancreas transplantation has been used to aid patients with Type II diabetes.[224]

CHALLENGES

There is a lack of knowledge regarding the way stem cells behave in the body following the transplantation. Post-transplantation, cells derived from pluripotent stem cells may go out of control and become cancerous in the patient's body, making these procedures inherently risky. Another hurdle to overcome pertains to the observation that the majority of implanted or administered stem cells do not graft. Currently, there is not sufficient evidence for the efficacy of most stem cell treatments, despite some clinics advertising the treatment's alleged efficacy.

For transplantations of tissues and cell types other than stem cells, other issues emerge, such as engineering difficulties: it is difficult, for example, to create 3D tissues and organs for transplantation. While 3D printers have been suggested as a way to create such tissues, this field is still in its infancy. Another persistent challenge is the need to procure tissues and cells from human donors, who are almost always in short supply. Transplant rejections (due to immune mismatch between donor and recipient) are prevented by the use of immunosuppressive drugs, but these carry risks of their own, and leave the donors more susceptible to infectious diseases and cancers.[225] 3D bioprinting, or growing an organ from the patient's own cells, represents a promising alternative to donor transplants. Human organs grown in chimeric animals, or engineered stem cells that are resistant to immune rejection, could provide solutions to transplant rejection.



Lifestyle Interventions

RELEVANT OBSTACLES

- Accessibility of Treatments
- Social Perceptions of Aging and Biases Against Aging
- Genomic Instability
- Deregulated Nutrient-Sensing
- Mitochondrial Dysfunction
- Cellular Senescence
- Altered Intercellular Communication & Inflamm-aging
- Changes in the Extracellular Matrix

SUMMARY

There are many lifestyle interventions that can increase longevity. These include good sleeping habits, physical exercise, healthy eating, positive thinking, limiting stress, and others. In this section we focus on physical exercise. We will also cover caloric restriction—an extreme variation of healthy eating—as a different remedy, because of the great difficulty involved in adopting that lifestyle.

Physical exercise can counter mitochondrial dysfunction, reduce inflammation and the deregulation of nutrient-sensing pathways, and alleviate and postpone aging-related conditions like sarcopenia, cardiovascular diseases and even cognitive decline.

DESCRIPTION

It has been established that physical activity and endurance training provide considerable benefits to mitochondrial function.[226] Physical exercise promotes mitochondrial biogenesis (i.e., increase in mitochondrial mass), turnover, degradation and clearance of damaged mitochondria.[227]

Physical exercise leads to improved mitochondrial function, which is suspected of being associated with an increase in life expectancy.[228] This association has been further cemented by the insight that muscle strength could be used as a biomarker of aging,[229] following research on nearly 140,000 participants from 17 countries.[230] Among top athletes, it seems that physical exercise also imparts remarkable longevity: one Lancet study revealed that 90% of elite runners have exceeded the life expectancy in their nations by an average of 12 years.[231] This evidence is controversial, however, as elite athletes may simply enjoy good genetics that provide them with a better metabolism.

The main protection that endurance training endows to humans is against sarcopenia, cardiovascular diseases and cognitive deterioration.[232] Lifelong aerobic exercise has also been shown to protect against inflamm-aging in mice.[233] Physical exercise can even affect the reorganization of the extracellular matrix.[234] Finally, physical activity promotes healthy functioning of the immune system and thereby can prevent or mitigate senescent cell accumulation and cancer formation.[235] [236] [237]

IMPORTANCE FOR OVERCOMING OBSTACLES

Thanks to our relatively strong understanding of the benefits of physical exercise, it can help to mitigate the consequences of our lack of scientific understanding of the mechanisms of aging. We do not, for example, sufficiently understand the precise mechanisms by which the mitochondria impact the aging process to develop sophisticated drugs to counter those mechanisms. Instead, simple physical exercise offers a cheap and widely accessible solution.

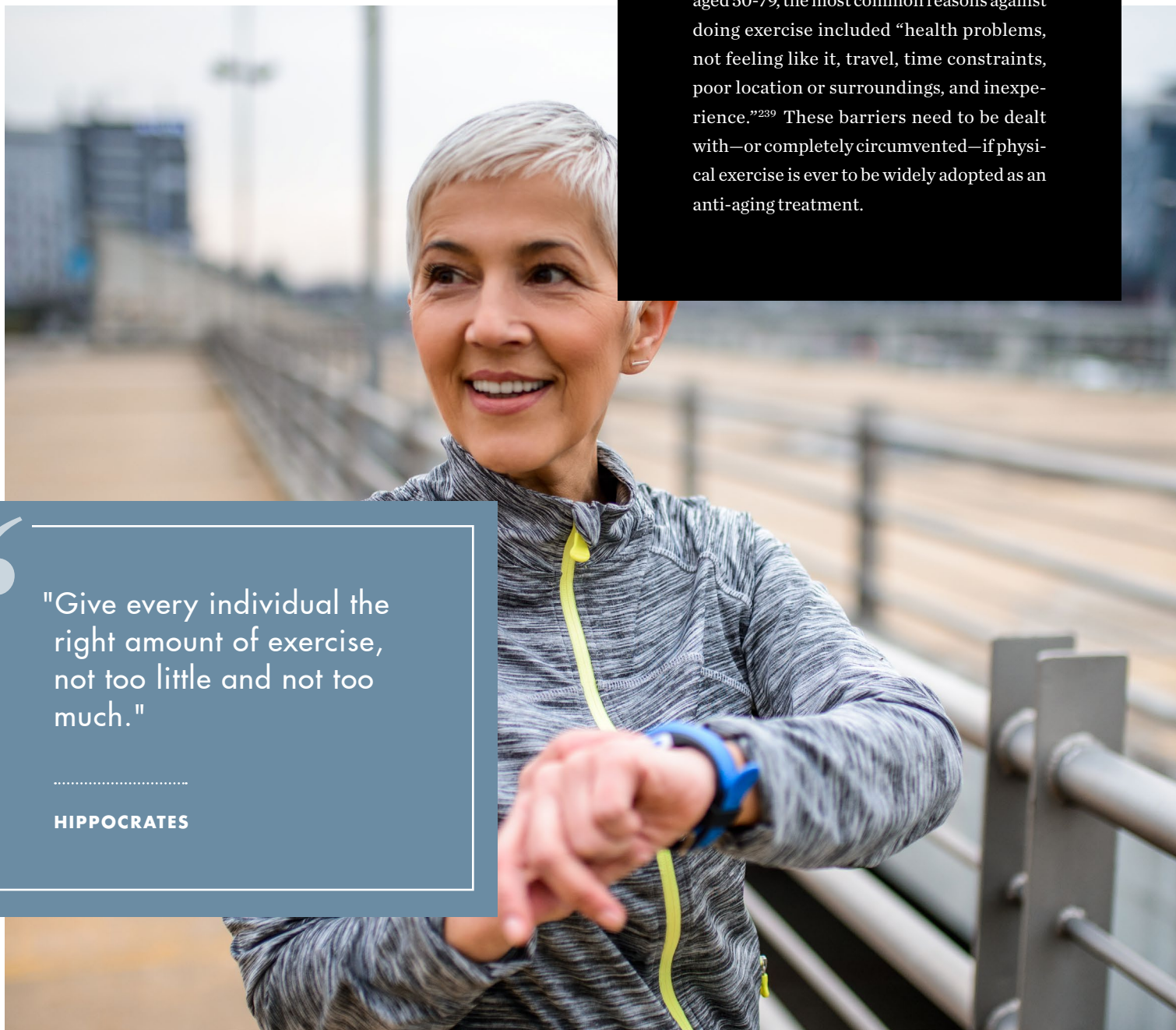
CURRENT STATUS AND USES

Physical exercise is often prescribed by medical doctors worldwide, but is just as often disregarded by patients. In the U.S., fewer than 5% of adults undergo daily physical exercise training of

30 minutes or more. Only one-third of all adults are in compliance with the recommended physical exercise regimen.[238] It is therefore clear that while there is wide recognition that physical activity can help to prevent aging-related conditions and diseases, many adults—at least in developed countries—are either unwilling or unable to make full use of this relatively simple treatment.

CHALLENGES

Physical exercise has been shown to successfully extend healthspan and lifespan, but not everyone makes use of it. The main challenge is motivating people to do it. In a survey conducted by the U.S. AARP among adults aged 50-79, the most common reasons against doing exercise included "health problems, not feeling like it, travel, time constraints, poor location or surroundings, and inexperience."[239] These barriers need to be dealt with—or completely circumvented—if physical exercise is ever to be widely adopted as an anti-aging treatment.



> "Give every individual the right amount of exercise, not too little and not too much."
>
> **HIPPOCRATES**

Hormesis-Promoting Treatments

RELEVANT OBSTACLES

- Telomere Attrition
- Loss of Proteostasis
- Deregulated Nutrient-Sensing
- Mitochondrial Dysfunction
- Cellular Senescence
- Altered Intercellular Communication and Inflamm-aging

SUMMARY

The term "hormesis" is used in biology to describe cases in which certain substances or stimuli at low doses can invoke a stress response in the body, which then leads—seemingly counterintuitively—to an extension of the organism's healthspan and lifespan. Higher doses of the same stimuli, however, cause damage to the body.[240]

Cellular and bodily systems constantly strive to stay at a state of hormesis, in which they reach their optimal performance. Some of these hormesis-ensuring mechanisms, however, may become degraded in the aging process. Since there are several examples of aging-related hormesis, we've chosen to focus on just one in this work: mitohormesis.

Mitochondrial dysfunction is one of the indicators of aging, but a certain level of mitochondrial stress can counterintuitively improve the health of cells, organs and even the entire organism. The process in which the cell responds to mitochondrial stress in a positive way is called mitohormesis, and is currently being studied as a potential remedy both to mitochondrial dysfunction and to the aging process itself.

DESCRIPTION

Mitohormesis describes a positive hormetic response to mitochondrial stress that promotes longevity and health.[241]

Mitohormesis, induced by an increase in the level of reactive oxygen species (ROS), has been shown to extend the lifespan of nematodes, fruit flies, fish and mice.[242] Interestingly, mitohormesis can also be caused by caloric restriction, suggesting that it may explain some of the positive effects caloric restriction has on extending lifespan.

There are various explanations for mitohormesis' impact on longevity. The most plausible seems to be that mitohormesis works by increasing the level of mitochondrial ROS production, which provokes a cellular stress response that upregulates genes that are associated with longevity.[243] Other mechanisms may also be responsible for the positive effects of mitohormesis, such as a dysfunction of the mitochondrial respiration process—which also extends lifespan in nematodes.[244]

IMPORTANCE FOR OVERCOMING OBSTACLES

Mitohormesis proves that certain low levels of mitochondrial dysfunction can be harnessed for extending healthspan and lifespan, instead of harming the body. It also demonstrates the important role well-developed scientific models must play in any attempt to alter the aging process, since simply trying to mitigate mitochondrial dysfunction by way of antioxidants could actually shorten lifespan instead of extending it.[245]

CURRENT STATUS AND USES

Exposure to stimuli that induce mitohormesis, like ROS, has been shown to increase lifespan and healthspan in several organisms, and improve human health as well.[246] Certain compounds like glucosamine,[247] metformin,[248] and sulfophane,[249] among many others, apparently have a beneficial effect via mitohormesis. A ketogenic diet can induce mitochondrial damage, and thus lead to mitohormesis,[250] as can exercise and especially high-intensity interval training.

CHALLENGES

Besides these relatively mild options, treatments based on mitohormesis have not yet reached the market. One consideration for an effective mitohormesis treatment is the ability to carefully balance the damage done to the cells by mitochondrial dysfunction and the induced stress responses that provide health benefits. Furthermore, different cells in different tissues may have widely different responses to stimuli that induce mitohormesis.

Supplementation with Biomolecules

RELEVANT OBSTACLES

» Genomic Instability

» Telomere Attrition

» Mitochondrial Dysfunction

» Stem Cell Exhaustion

SUMMARY

Supplementation with biological molecules encompasses many substances like melatonin, creatine, vitamins and NAD precursors. We focus on NAD precursors in this section, as there is good evidence that their dietary administration can protect animals—and possibly humans—from aging-related diseases and conditions. NAD precursors are currently being sold over the counter as a dietary supplement, and are being tested in several clinical trials.

DESCRIPTION

Nicotinamide adenine dinucleotide (NAD) is a metabolite, a signal molecule and an energy carrier in cells.[251] The presence of NAD is vital for many biological processes in the cell, while NAD-deficiency is correlated with aging-related diseases and conditions such as neurodegeneration and cancer. Furthermore, NAD levels have a direct impact on the activity of sirtuins, which regulate organisms' lifespan.[252]

Administration of NAD precursors (substances that are transformed inside the body into NAD) has reduced aging-related decline in mice tissues.[253] There is clear evidence that NAD precursors, taken as part of the daily diet, can elevate NAD levels in aged tissues and in the cells. These elevated levels lead to better protection from aging-related conditions and diseases in mice.[254]

IMPORTANCE FOR OVERCOMING OBSTACLES

NAD administration is especially promising since it can be sold as a food supplement, and thus does not have to undergo the onerous FDA approval process.

High levels of NAD may contribute to longevity and healthspan by various mechanisms, including:

» Promoting telomere elongation[255]

» Taking part in DNA repair[256]

» Countering stem cell aging-related reduced functionality[257]

CURRENT STATUS AND USES

Several clinical trials are currently underway, in an attempt to demonstrate the beneficial effects of elevated NAD levels in human beings. So far, the trials have mostly proved that NAD precursor supplements cause no damage to the body.[258] There is currently no clinical proof, however, that NAD precursor supplementation has any beneficial effect for humans, although this has not stopped several companies from selling NAD precursors as an anti-aging supplement.[259] NAD precursors do not seem to have any short-term negative side effects, though, and—based on experimental results in animals—seem likely to indeed have some positive effect on humans as well.

CHALLENGES

The precise mechanisms by which NAD precursors are transported across cellular membranes are not yet clear, potentially hindering treatment efficacy. Additionally, it is unclear how NAD is metabolized in different tissues, and it is quite possible that every tissue needs different levels of NAD.[260]

Treatment by administration of NAD precursors has so far only proven its value in model organisms. It remains unclear if they are beneficial for human beings as well.

Finally, there is the issue of negative public perception: administration of NAD precursors is still often viewed as unnecessary and as a treatment option reserved mainly for longevity enthusiasts.

Quantified-Self Apps, Wearables, Embeddables and Ingestibles

RELEVANT OBSTACLES

» Slow Pace of Drug Development and Approval

» No Set of Agreed-Upon Biomarkers for Quantifying Biological Age

» Deregulated Nutrient-Sensing

» Mitochondrial Dysfunction

SUMMARY

People use wearables, ingestibles and embeddables, together with quantified-self apps, to quantify their physiological biomarkers, habits, moods and behaviors. In this way, they can acquire new and healthy habits—like meditating, exercising, or improved nutrition—or identify certain biomarkers, like sleep patterns, that could be related to the aging process. Quantified-self apps and gadgets could also help collect the data needed to streamline the discovery and approval process of new life extension drugs.

DESCRIPTION

Wearables, embeddables and ingestibles are all devices that can be used to constantly track certain physiological parameters, as well as activities, location, and social behavior. The Federal Communications Commission has defined these devices the following way:[261]

» **Ingestibles** are wireless devices that can be swallowed, like smart pills that monitor a user's physiological reaction to a certain medication, or track the level of said medication in the blood.[262] Ingestibles may also include sophisticated sensors, like Medtronic's pill-shaped video cameras.[263]

» **Wearables** are digital tools that can be worn on the body to monitor heart rate, breathing, activity and other vital signs. Wearables appear today in many different types of clothing, including watches, T-shirts, belts, hats, pants, shoes, and glasses.[264] They can even be implemented in the form of electronic tattoos—thin sensors that collect data from the skin and can be peeled off after use.[265]

» **Embeddables** are tiny devices implanted in the body, whether for therapeutic purposes (e.g., heart pacemakers, insulin pumps, or a drug-releasing pill[266]) or for monitoring vital signs like blood sugar levels.[267]

Many users use their smartphones as mobile hubs for the data obtained by wearables, ingestibles and embeddables, and utilize apps that analyze the data and communicate it, sometimes with recommended actions, to the user and/or their primary care physician.

The combination of abundant smart sensors and end-user tools to make sense of the data creates quantified-self individuals: people who are constantly aware of the inner workings of their body and of any change in their biological parameters, sometimes within seconds of its occurrence.

IMPORTANCE FOR OVERCOMING OBSTACLES

As wearables, ingestibles and embeddables become commonplace, they are likely to be used to overcome some of the obstacles to longevity, like deregulated nutrient pathways. Apps like Zero Fasting Tracker, for example, can be used to track users' eating habits and help them undergo a dietary restriction regimen,[268] while embeddables like pacemakers and insulin pumps can mitigate the negative effects of some aging-related diseases.

Smart sensors can also help collect data about vital signs and biological parameters from the body. These data could then be used by pharmaceutical and biotechnology firms and start-ups to identify new biomarkers for aging, or better understand existing ones. Smart sensors can also be used to conduct and supplement

clinical trials on a large scale, by easily obtaining large amounts of data from participants. Thus, they could aid in expediting the drug development and approval processes. They can also be helpful in collecting DNA and health data from centenarians and supercentenarians.

CURRENT STATUS AND USES

According to eMarketer, nearly a quarter of U.S. adults will make use of a wearable device in 2019. The penetration rate is higher for 25-34 year-old consumers, 38% of whom will use wearables. Currently the most common wearable is the smartwatch.[269] Use of ingestibles is also expected to soar.[270] Meanwhile, embeddables like deep brain stimulators, pacemakers and insulin pumps are widely used by patients, and are expected to become even more efficient and useful.

The Quantified Self movement has grown alongside the progress made in the personal sensors field. It encourages people to collect and analyze data from their daily lives. As of early 2019, the Quantified Self movement has nearly one hundred thousand members in 223 meetup groups.[271]

CHALLENGES

Adoption of wearables is growing, but slowly. People mainly use ingestibles and embeddables to track diseases and unhealthy physiological conditions. This is possibly the result of the high price of wearables, which is often multiple times higher than that of an ordinary corresponding piece of clothing. In the case of ingestibles and embeddables, there are significant side effects and risks associated with the ingestion and implantation of such devices in the body. As long as this is true, it is unlikely that these “insidables” will be widely adopted. Furthermore, as ingestibles and embeddables are under strict governmental regulation, the research and development process required to approve any new device is long and arduous.

Finally, it should be noted that these technologies sometimes suffer from negative public perception, as many people are concerned with privacy issues, and believe that by using wearables, embeddables and ingestibles they are opening themselves up for surveillance or hacking.

Blood-Based Treatments

RELEVANT OBSTACLES

» Genomic Instability

» Stem Cell Exhaustion

» Altered Intercellular Communication and Inflamm-aging

» Changes in the Extracellular Matrix

SUMMARY

Blood donations from young donors may contain growth factors and other molecules that rejuvenate old tissues. While old mice become rejuvenated following an injection of young blood or bloodborne proteins, the technique has not been sufficiently tested yet in human beings.

DESCRIPTION

Parabiosis is the procedure of connecting the blood systems of two animals—in this context, a young and an old one—so that each shares the blood supply and circulation of the other. This technique was shown in 2005 to enhance muscle regeneration in old mice connected to young ones, apparently due to the activation of progenitor cells in the old mice's tissues.[272]

Follow-up studies of parabiosis demonstrated a reversal of age-related cardiac conditions in old mice, allegedly due to the presence of an antihypertrophic factor (growth differentiation factor 11, or GDF11) in the young partner's blood.[273] When this factor was distilled from the blood of young mice, and injected daily into old mice, a similar rejuvenation effect was produced.

The same growth factor reduces DNA damage in satellite cells, boosts the growth and creation of young blood vessels and neuronal growth, and activates stem cells in order to repair injuries to the body.[274] It also has an effect on skin biology and encourages production of extracellular matrix components, which may aid in rejuvenating the skin.[275]

There is still controversy about the exact role GDF11 plays in the rejuvenating effects of parabiosis, with at least one group claiming that GDF11 in fact *inhibits* skeletal muscle regeneration.[276] Regardless, there seems to be widespread agreement that parabiosis can have beneficial effects in some model animals—whether via GDF11 or other factors.[277] Furthermore, these studies demonstrated that old tissues can be rejuvenated even without actually connecting two circulation systems together.

IMPORTANCE FOR OVERCOMING OBSTACLES

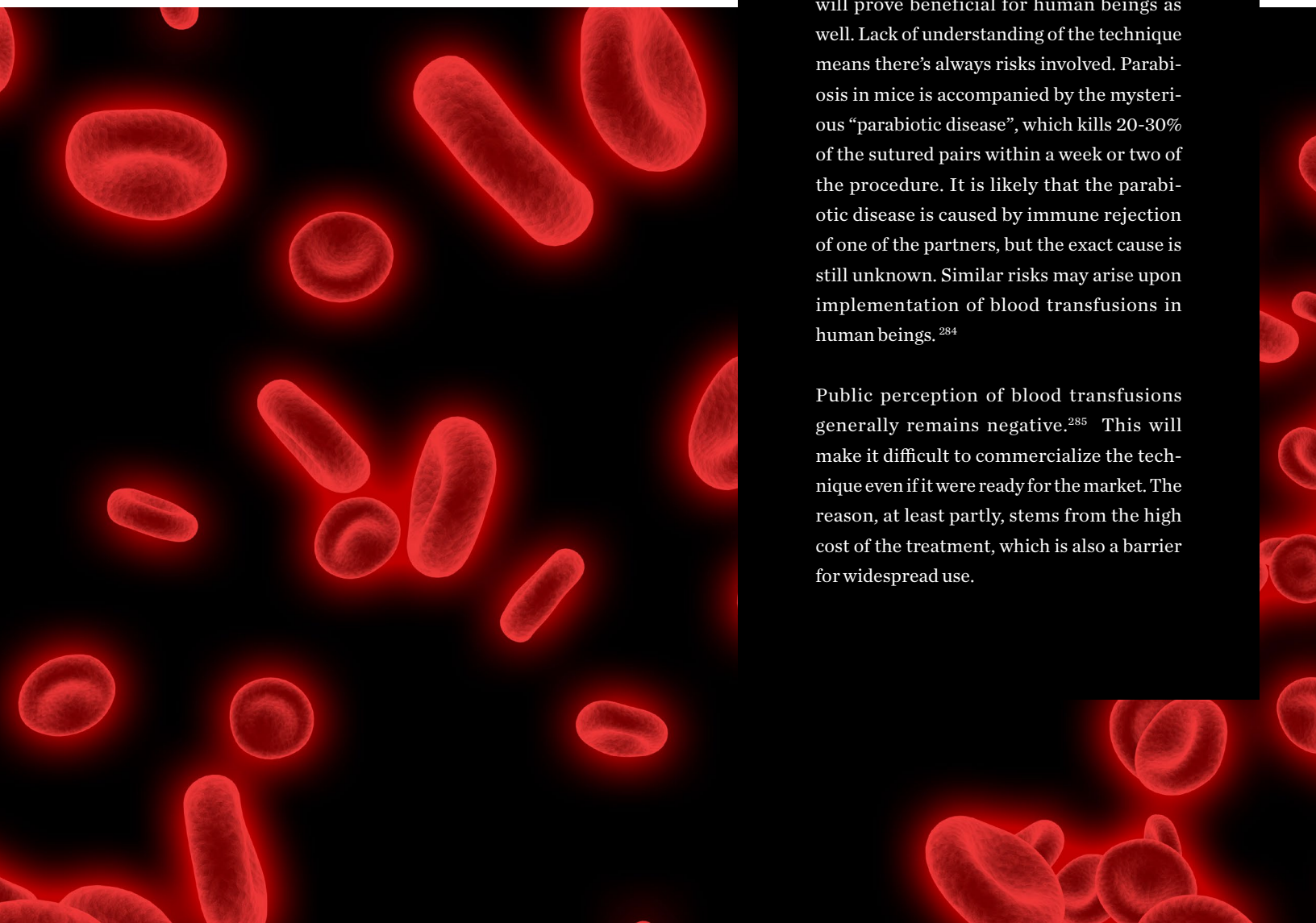
While more research into the mechanisms of parabiosis is obviously needed, blood transfusions have already demonstrated their efficacy in mice, and may prove beneficial to human beings as well. However, while the initial treatments may be based on actual blood transfusions from young donors, it is most likely that as the research moves along, the exact factors in young blood that promote tissue rejuvenation will be discovered, analyzed and synthesized in labs and factories to increase accessibility for all.

CURRENT STATUS AND USES

Parabiosis is still undergoing testing, with several companies already trying to translate the insights gained from parabiosis experiments in mice to anti-aging treatments for humans. Elevian, for example, is a startup that's experimenting with GDF11 injections as a way to treat aging-related diseases.* They are currently at the preclinical phase for treatments to coronary heart disease, type II diabetes, and Alzheimer's disease, and are researching whether GDF11 can help prevent or mitigate sarcopenia symptoms.[278] The company raised $5.5 million in seed money in late 2018.[279]

*Disclaimer: Dr. Peter Diamandis, XPRIZE's Founder and Executive Chairman, is also one of the funding advisers **of Elevian.**

Another company, Alkahest, attempts to treat aging-related cognitive decline, as well as neurodegenerative diseases, using "beneficial rejuvenating factors in young plasma", as described on the company's website.[280] The company received an investment of $37.5 million from Grifols, itself a producer of plasma therapies.[281] A third company, Ambrosia, provided its elderly customers with plasma donations from young donors. Ambrosia rose to infamy following media coverage that depicted it as a vampiric startup "...harvesting the blood of the young."[282] Following the FDA's 2019 warning against plasma infusions from young donors, Ambrosia halted its patient treatments indefinitely.[283]



CHALLENGES

It is as yet unknown how exactly young blood rejuvenates old tissues, which factor or groups of factors have the most prominent effect, or the best dose. Young blood transfusions have only proven their worth in model organisms, and not on humans yet. It is therefore impossible to know for certain whether or not they will prove beneficial for human beings as well. Lack of understanding of the technique means there's always risks involved. Parabiosis in mice is accompanied by the mysterious "parabiotic disease", which kills 20-30% of the sutured pairs within a week or two of the procedure. It is likely that the parabiotic disease is caused by immune rejection of one of the partners, but the exact cause is still unknown. Similar risks may arise upon implementation of blood transfusions in human beings.[284]

Public perception of blood transfusions generally remains negative.[285] This will make it difficult to commercialize the technique even if it were ready for the market. The reason, at least partly, stems from the high cost of the treatment, which is also a barrier for widespread use.

Minerals Supplementation

RELEVANT OBSTACLES

» Genomic Instability

» Deregulated Nutrient-Sensing

» Altered Intercellular Communication and Inflamm-aging

» Changes in the Extracellular Matrix

SUMMARY

Aging alters the body's capacity to absorb and retain certain minerals, including phosphates, calcium, and zinc. In this analysis we focus only on zinc, though, as a representative for this class of remedies.[286]

Aging reduces the body's capacity to uptake zinc from the gastrointestinal tract (aka "the gut"), leading to zinc deficiency in many older adults. Zinc deficiency is associated with thymic degeneration and immune system malfunction. Elevating zinc levels, however, can improve the activity of the immune system, induce DNA repair, rejuvenate the thymus and protect from age-related macular degeneration.

DESCRIPTION

Normal zinc levels contribute to the healthy functioning of the immune system, the thymus, antioxidant activity and over 200 enzymes.[287] The aging body, however, suffers from a decreased capacity to absorb zinc from food. According to some estimates, approximately 40% of the elderly population in the U.S. suffers from zinc deficiency.[288]

Zinc deficiency leads to thymic degeneration, which directly affects the immune system.[289] Zinc dietary supplementation, however, can increase zinc levels in tissues and cells,[290] thus mitigating the aging body's declining capacity to absorb zinc.

IMPORTANCE FOR OVERCOMING OBSTACLES

There is evidence that zinc, when administered as a dietary supplement, can extend the life expectancy of mice, mainly because of a decrease in the incidence of cancer and infection at old age.[291] Several studies show that dietary zinc supplementation improves the functioning of the immune system in elderly humans,[292] induces DNA repair, aids in extracellular matrix calcification (increasing bone strength),[293] rejuvenates the thymus and protects from age-related macular degeneration (AMD).[294]

CURRENT STATUS AND USES

Zinc is being used widely as a dietary supplement, and can be found in nearly all multivitamin dietary supplements.[295] Even firms that advocate for dietary supplements, however—like InsideTracker, which is dedicated to analyzing biomarkers in human beings—conclude that people should not take zinc supplements without first assessing their zinc blood levels.[296]

CHALLENGES

Zinc supplementation can be toxic at high doses, explaining the recommendation that people refrain from taking zinc supplements unless they know they're suffering from a deficiency. [297] It's unclear how much zinc is needed to have a positive effect, especially as people get older and their zinc uptake capacity changes. [298] While several forms of dietary supplements are currently being sold for zinc, it is unclear which formula is best. [299]

Dietary Restriction and Intermittent Fasting

RELEVANT OBSTACLES

- Deregulated Nutrient-Sensing
- Mitochondrial Dysfunction
- Cellular Senescence
- Changes in the Extracellular Matrix

SUMMARY

Dietary restriction and intermittent fasting can significantly extend healthspan and lifespan in various organisms, and have beneficial effects for human beings as well. Many find it difficult, however, to sustain such a dramatic lifestyle constraint.

DESCRIPTION

Dietary restriction is known to have a significant impact on the healthspan and lifespan of various organisms, including yeast, nematodes, fruit flies, mice and even primates like rhesus monkeys.[300] Benefits in human beings include reversal of insulin-resistance state in Type II diabetes patients,[301] production of fewer reactive oxygen species, and improvement in biomarkers that are related to aging, such as DNA damage and thyroid hormone levels.[302] In animal models, benefits include improvement of cognitive function and brain structure in mice,[303] and amelioration of aging-related behavioral deficits in a mouse model of Alzheimer's disease.[304] In rats, caloric restriction has been shown to improve extracellular matrix biosynthesis.[305] Dietary restriction provides these benefits at least partly via altering the activity profile of the mitochondria, apparently staving off mitochondrial dysfunction.[306]

Dietary restriction usually entails reducing daily calorie intake by 20-40%.[307] This reduction can be achieved by simply reducing the amount of food consumed, or by means of intermittent fasting. Practitioners of intermittent fasting may fast for 16 hours or longer every day (usually including nighttime), for 1-2 days every week, or even every other day.[308] Both intermittent fasting and reduction of food consumption are believed to have health and longevity benefits.

IMPORTANCE FOR OVERCOMING OBSTACLES

Much like physical exercise, dietary restriction provides an easily available treatment that most people can (at least in theory) use. Although the efficacy of such treatments would likely be improved by a better understanding of the underlying physiological mechanisms, even the currently accepted methods for dietary restrictions seem to have a positive effect on human healthspan, and quite possibly on lifespan as well.

CURRENT STATUS AND USES

It is unclear just how many people choose to practice dietary restriction, and even less clear how many of those actually maintain this restriction over time. There are some associations and societies that encourage people to take up dietary restriction and offer them communal support. These include CR Society International[309] and the WeFa.st forum erected by the anti-aging firm HVMN.[310]

CHALLENGES

This remedy is almost certain to be beneficial in human beings, but cannot be implemented on a mass scale before a better understanding of its underlying mechanisms is reached. Moreover, it remains difficult to figure out the best, ideally personalized, dietary restriction regimen for people to employ—especially when the wrong diet could cause serious harm to practitioners. Furthermore, dietary restriction of any kind requires determination, willpower and grit—traits that unfortunately are often in short supply.

Senolytic and Senomorphic Therapies

RELEVANT OBSTACLES

» Cellular Senescence

» Altered Intercellular Communication and Inflamm-aging

» Changes in the Extracellular Matrix

SUMMARY

Senolytic therapies are drugs that eliminate senescent cells, while senomorphic therapies reduce their negative impact on the body. Several such drugs, senomorphic therapies like rapamycin and metformin, are currently being tested in clinical trials. Senolytic effects of certain already existing drugs, such as Azithromycin, are also being investigated. [311]

DESCRIPTION

Senolytic and senomorphic therapies—together, *senotherapeutics*—represent a relatively new field of medical research, which attempts to counteract the negative effects that senescent cells have on the body.[312] Cellular senescence was previously thought to be beneficial for the body, and while it is still considered a normal biological function, the chronic accumulation of senescent cells is associated with aging-related diseases and conditions, including cancer, metabolic disorders, obesity, diabetes, and cardiovascular and neurodegenerative diseases.[313]

The two main senotherapeutic approaches are:

» **Senomorphics:** Agents that inhibit or interfere with the *senescence-associated secretory phenotype* (SASP) by which senescent cells cause inflamm-aging. Rapamycin, one of the most notable drugs in this group, has been shown to inhibit SASP, improve health and extend longevity in several species, including mice and potentially dogs.[314] Other promising drug candidates in this group include metformin,[315] which has been shown to delay the onset of aging-related pathologies like diabetes, and is currently being tested in clinical studies.[316]

» **Senolytics:** Drugs that eliminate senescent cells in the body. Some senolytic drug candidates like fisetin, ABT263, and dasatinib have demonstrated efficacy in animal models. In such models, these drugs have rejuvenated aged hematopoietic and muscle stem cells,[317] reduced senescence markers in multiple tissues and age-related pathology, and extended lifespan.[318]

Senolytics are currently closer than senomorphics to being approved for human use. Other methods, however, for eliminating senescent cells are also being tested in labs. One of those methods relies on the engineering of mammalian cells so that they can seek out senescent cells and eliminate them.[319] It is highly likely that many other innovations in senolytics will emerge in the near future.

IMPORTANCE FOR OVERCOMING OBSTACLES

Senotherapeutics can be used to eliminate senescent cells or reduce their negative impact on the body. As senescent cells contribute to the aging process and to inflamm-aging, senotherapeutics could slow down the aging process and postpone aging-related conditions and diseases.

CURRENT STATUS AND USES

There are several senotherapeutics currently under research and development, like metformin, fisetin, and rapamycin, as well as several companies in the space, including Cleara Biotech and Unity Biotechnology. Fisetin is currently being evaluated in clinical trials conducted on older adults to understand whether it can alleviate frailty and inflammation.[320] [321] Metformin is expected to be studied in a large-scale clinical trial called *Targeting Aging with Metformin* (TAME).[322] Early clinical trials with rapamycin held on healthy seniors have shown promising initial results, with no significant side effects.[323]

Even if these clinical trials were to succeed, however, it is unlikely that senotherapeutics would be provided by medical practitioners with the formal purpose of extending lifespan; it is more likely they would be used as a preventative medicine to decrease old people's chances of contracting aging-related diseases and pathologies. Given that fisetin is already available as a relatively inexpensive supplement, however, it is possible that early adopters will still be able to use it even without medical supervision.

CHALLENGES

Several senotherapeutics are currently in a testing phase, but numerous challenges must be resolved if these methods are to develop into a mature treatment category. More senescence biomarkers must be identified and utilized to assess the level and impact of senescent cells in the body, and to target senescent cells. The fact that different types of senescent cells exist needs to be further explored.

There is also a need to better understand senescence-inducing mechanisms in cells, and the impact of SASP on the body so that it might be counteracted. Better models of the interaction between senescent cells in different tissues also must be devised, as the chemical signals released by senescent cells in one tissue can affect and complement those in other tissues. Also, the senotherapeutic effects of existing drugs have to be identified, and it should be established which ones of these drugs should be undergoing new clinical trials and can be repurposed for prevention of aging-related diseases.

Thymic Rejuvenation

RELEVANT OBSTACLES

» Genomic Instability

» Cellular Senescence

» Altered Intercellular Communication and Inflamm-aging

SUMMARY

Thymic rejuvenation treatments may reverse the atrophy and decline of the thymus in older adults, and thereby restore immune system activity.

Thymic rejuvenation may be seen as one part of the overarching Cell and Tissue Replacement Therapies remedy. Indeed, the thymus is not the only factor to blame for the aging-related decline of the immune system; other factors, like stem cell depletion, telomere shortening, and clonal expansion of specific immune cells are also to blame. In this remedy, however, we focus specifically on the thymus because of its unique involvement in the consistent function of the immune system—which has direct consequences on the aging process

DESCRIPTION

As human beings age, their thymus undergoes atrophy and declines in function (a process also known as involution).[324] Since the thymus is an essential part of the immune system, its loss of function leads to a significant decline in the functioning of the immune system.[325]

Thymic rejuvenation has been demonstrated in several ways, including:

» Sex steroid inhibition, which can be achieved by castration and other means. The inhibition influences the thymus and restores its function in mice[326]

» Restoration of the thymic epithelium, an effect that has been achieved by administration of the FDA-approved drug Palifermin. Palifermin is often prescribed to patients with a need to protect and rejuvenate sensitive mucous membranes, usually due to chemotherapy and radiation regimens[327]

» Reversal of aging-related thymic involution, which has been achieved by administration of the hormone ghrelin (GRL) in old mice[328]

» Stimulating proliferation, differentiation and survival of the thymus cells, usually via molecular signals like Interleukin-7 and Interleukin-22[329]

IMPORTANCE FOR OVERCOMING OBSTACLES

Rejuvenation of the thymus may aid in restoring the function of the immune system. As the immune system is in charge of suppressing and eliminating cancerous and senescent cells in the body,[330] this remedy may help minimize the incidence of cancer, frailty and susceptibility to infectious diseases in old people, as well as slow down the pace of aging itself due to the elimination of senescent cells.

CURRENT STATUS AND USES

This remedy is still being tested for efficacy and safety in animal models.[331] The startup Repair Biotechnologies is attempting to reverse thymic atrophy, and is currently still proving the treatment's efficacy on animal models. Another company, Intervene Immune, is examining potential ways to rejuvenate the thymus. [332]

The FDA-approved drug Palifermin is used for other purposes at the moment, but has the potential to also reduce thymic involution. [333] However, its beneficial effects on the thymus have not been verified in clinical tests.[334]

CHALLENGES

The precise mechanisms underlying thymic atrophy, its effects on the immune system and on aging, and its rejuvenation are not clear yet. There are also inherent risks, as is the case with any treatment that induces cell proliferation and rejuvenation. Thymus rejuvenation techniques have a good chance of raising the risk for cancer in treated patients. Lastly, thymus rejuvenation treatments have only proven their worth in model organisms, and not on humans yet. It is therefore impossible to know for certain whether or not they will prove beneficial for human beings as well.

WHAT IS THE THYMUS?[335]

The thymus is a small organ in the body with some very important functions. Located just below the breastbone, it is part of the body's lymphatic system as well as the endocrine system.

The primary role of the thymus is producing progenitor cells that mature into T-cells. These cells play a vital part in helping destroy infected or cancerous cells. T-cells also help other organs in the immune system grow properly, as it is the primary donor of cells for the lymphatic system.

This mighty organ is proportionately large in infants, and grows until puberty. It naturally starts to shrink and becomes less important for bodily function over adulthood.

Human Epigenomics Mapping

RELEVANT OBSTACLES

» Slow Pace of Drug Development and Approval

» Epigenetic Alterations

SUMMARY

Epigenetic changes affect gene expression, instead of changing the genetic code itself. The results of this method are thus easier to reverse than genetic engineering. Epigenetic alteration of human cells could conceivably provide protection from several aging-related diseases and conditions.

DESCRIPTION

Epigenetic alterations are one of the indicators of aging. They occur constantly in every cell in the body, but most of them are in fact irrelevant to aging and have no negative impact. In order to pinpoint the injurious and aging-related epigenetic alterations—and understand how to counter them—the scientific community needs a better understanding of the epigenetic processes that occur in each cell. Such understanding would be invaluable for enabling epigenetic corrections of cellular activities of all sorts (e.g., activating telomerase to counter telomere attrition, forcing senescent cells to undergo apoptosis, or rejuvenating cells if their genome has not been severely damaged). This could have an impact similar to that of genetic engineering—but in a way that is more transient and easier to undo, and therefore less risky.

The field of epigenomics searches for a better understanding of these epigenetic cellular processes. Epigenomics researchers focus on the various factors that regulate gene expression, which can, for example, cause a cell to divide or become senescent or cancerous. Several projects currently underway aim to catalogue the various epigenetic mechanisms in human cells.[336]

IMPORTANCE FOR OVERCOMING OBSTACLES

With an "epigenetic map" that describes the constant epigenetic changes in the cell, as well as their causes and implications, researchers can develop:

» Better models to understand the aging process[337]

» Epigenetic-level engineering of human cells, with the power of genetic engineering to silence or overexpress certain genes, but in a more transient manner, and which is less likely to pass to the next generation[338]

» Measures to counter the effect of certain environmental factors that can affect the aging process, like pollutants or malnutrition (which can increase susceptibility to various diseases, even in subsequent generations)[339]

» Treatments that emulate the epigenetic effect of lifestyle remedies, such as dietary restriction and physical exercise[340]

CURRENT STATUS AND USES

Several projects designed to map the epigenome of human cells were initiated in recent years. These include:

» The Encyclopedia of DNA Elements (ENCODE) project, which mapped many functional elements across the genome.[341]

» The NIH Roadmap Epigenomics Mapping Consortium, which builds on the results of the ENCODE project by conducting an integrative analysis of 111 reference human epigenomes.[342] The results were uploaded to publicly-accessible databases online, where they can be used by scientists and the general public.

CHALLENGES

The epigenome is not yet well understood, which makes it more difficult to fully map its workings. Even if the inner workings of the epigenome were all figured out, more efficient tools for analyzing the epigenome at a high level of resolution, and in real-time, are still missing.

Cognitive Enhancement for Improving Performance

RELEVANT OBSTACLES

» Governments Will Face Difficulties with Current Pension Laws

» Social Perceptions of Aging and Biases Against Aging

SUMMARY

Cognitive enhancement techniques and treatments are often used by the elderly in an attempt to improve their performance at work and in other arenas. While some of the techniques are controversial, it is clear that many old people are looking for cognitive enhancement tools.

DESCRIPTION

Aging is inevitably accompanied by a cognitive decline that is unrelated to aging-related neurodegenerative diseases.[343] It is clear, however, that many elderly people wish to improve their naturally declining cognitive functions.

Several techniques have been shown to improve cognitive health in the elderly. For example:

» *Improving sleep quality* can improve working memory, abstract problem solving and concentration.[344]

» *Good hydration* improves psychomotor processing speed, attention span and memory performance.[345]

» *Healthy nutrition* ensures that the brain has all the energy it needs to function properly.[346]

» *Brain training games* allegedly improve some aspects of cognitive function in older adults, especially sustained attention, working memory, and multitasking.[347] There are also claims, backed by peer-reviewed research, that they can lower the risk for dementia by up to 30%.[348]

» *Vitamin supplements*—especially ones that counter vitamin B and D deficiency, which is common in older adults—can improve cognitive performance and improve mood.[349]

» *Regular physical activity* slows aging-related cognitive decline.[350]

» *Certain pharmacological agents*—usually developed to treat neurological disorders—can improve cognition in older adults. These include modafinil (originally developed to counter narcolepsy), ritalin,[351] and drugs containing amphetamines like Adderall and Attentin, though they may bring negative side effects.[352]

» *Invasive and non-invasive brain stimulation* techniques, like transcranial direct current stimulation and deep brain stimulation, can improve cognitive function and attentional control in older adults.[353]

IMPORTANCE FOR OVERCOMING OBSTACLES

Improving cognition in older adults could result in improved performance—both at the workplace and in their general lives. This improved performance will help older adults maintain high work standards, sociability, and productivity, and over time can even minimize the social bias toward older people.

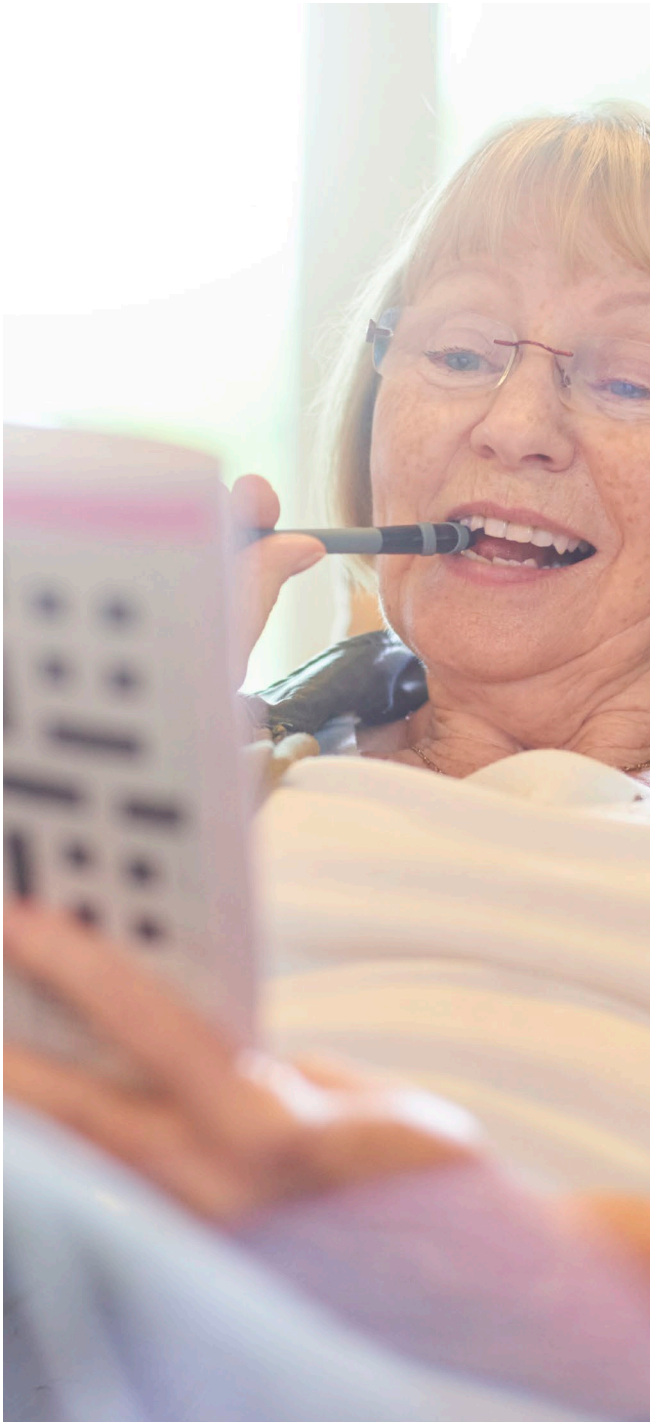
CURRENT STATUS AND USES

Without a doubt, brain training games are the most commonly utilized tool for cognitive enhancement in older adults, despite their controversial results. Lumosity, one of the leading apps in the field, had been used by 95 million people worldwide as of 2017.[354] Elevate, another highly popular app, was selected by Apple as "App of the Year" in 2014, and has been downloaded more than 15 million times.[355] That said, the actual beneficial effect these apps and games have is controversial at best, and Lumosity

was recently fined $2 million over unsubstantiated claims that its app could reverse symptoms of Alzheimer's disease.[356]

The popularity of cognition-enhancing drugs is also on the rise. While data on drug use comes mostly from young people, surveys show that the use of psychoactive drugs that improve performance, like modafinil, is rising. A 2016 survey conducted on 2,000 students in the UK revealed that one in every five students has used such drugs to study.[357] Many healthy adults are also "microdosing": taking miniscule doses of psychedelic drugs to augment their creativity and cognitive functions.[358]

Finally, early adopters are already experimenting with transcranial direct current stimulation,[359] but there are no official treatments for cognitive enhancement for the elderly.



CHALLENGES

The use of pharmacological agents like ritalin and modafinil carries an inherent risk to one's health. Ritalin, for example, has been shown to occasionally increase blood pressure and cause anxiety and insomnia.[360] Additionally, the precise mechanisms behind the workings of pharmacological agents, non-invasive brain stimulation, or brain training games, aren't well understood. As a result, the efficacy of some of these remedies is still highly controversial. While brain training games are considered to be low-risk, their application requires time, effort and willpower.

Finally, brain enhancing technologies and treatments can suffer from a negative reputation, particularly in the case of the more radical ones, like pharmacological cognitive enhancement or non-invasive brain stimulation.

Data Collection on Centenarians and Supercentenarians

RELEVANT OBSTACLES

» No Set of Agreed-Upon Biomarkers for Quantifying Biological Age

SUMMARY

Data about the lifestyles, genomes, epigenomes, microbiomes and other traits and characteristics of centenarians could greatly help the quest to understand the secrets to healthy aging and extended longevity. While there are several organizations dedicated to collecting information about centenarians, there is room to improve the methods of data collection and assimilation, and to expand these programs' outreach.

DESCRIPTION

Centenarians (100+ years old) and supercentenarians (110+ years old) may hold in their genomes and lifestyles some of the secrets to healthy aging. To uncover those secrets, data from a large number of centenarians must be collected, shared with the scientific community and pharmaceutical and biotechnological companies, and carefully analyzed.

IMPORTANCE FOR OVERCOMING OBSTACLES

Data collected from centenarians have already revealed some insights about healthy aging and the aging process in general. At least one analysis of centenarian genomes, for example, has revealed that centenarians and their offspring appear to maintain longer telomere length than others at comparable ages.[361] Other studies have developed the first "longevity-associated genes" and provided better understanding of genes like ApoE, mutations in which can dramatically increase risk for aging-related diseases.[362] Additional studies on data—biological or otherwise—collected from centenarians may therefore help us better understand longevity, the healthy aging process, and provide insights on quantifying biological age.

CURRENT STATUS AND USES

Over a dozen research groups are studying the centenarian phenotype and collecting data on centenarians.[363] The largest and most well-known groups and studies in operation today include:

» Okinawa Research Center for Longevity Science (ORCLS): The ORCLS has conducted research on the centenarians in the Okinawa area of Japan since 1975. By now it has conducted research on more than 900 centenarians, concentrating on their genetics, cognitive abilities, psychology, diet and other traits.[364]

» The New England Centenarian Study (NECS): The NECS has been recruiting centenarians and their family members since 1995, and is currently studying around 2,500 centenarians, 200 of which are supercentenarians.[365]

» The International Database on Longevity (IDL): The IDL is collecting data about super-centenarians from a group of 26 contributors from the academy. It currently contains data on about 18,685 semi-supercentenarians (over the age of 105) and 1,179 supercentenarians from 15 countries.[366]

FIGURE 4.3. THE WORLD'S CENTENARIANS

The World's Centenarians *As of 2015, there were nearly half a million centenarians on the planet. Where do they live?*		
COUNTRY	**TOTAL CENTENARIANS**	**CENTENARIANS/10K PEOPLE**
United States	72,000	2.2
Japan	61,000	4.8
China	48,000	0.3
India	27,000	0.2
Italy	48,000	4.1

Source: Pew Research Center, World's Centenarian Population Projected to Grow Eightfold by 2050 (2016)

CHALLENGES

Centenarians are extremely rare. The U.N. estimates that there are only around 316,000 living centenarians worldwide,[367] meaning only one in every 23,000 people or so makes it to their 100th year; it is no wonder that it's so difficult to find them! Even once they're located, it is difficult to keep track of their lifestyle choices and habits, as these are often tracked via smartphones and wearables. Very old people, however, often suffer from technological illiteracy, thus making it difficult to track their activity patterns. Finally, it is often difficult to verify the precise age of centenarians and supercentenarians.

Longevity and Life Extension Movements and Campaigns

RELEVANT OBSTACLES

- Misinformation About Longevity Treatments
- Concern of Overpopulation Straining Earth's Resources
- Slow Pace of Drug Development and Approval
- Governments Don't Classify Aging as a Treatable Condition
- Governments Will Face Difficulties with Current Pension Laws
- Ideological Objections
- Social Perceptions of Aging and Biases Against Aging

SUMMARY

Longevity and life extension movements provide information about the science and technology behind state-of-the-art treatments, work to alter public perceptions, and lobby for the legislation of longevity treatments at the national and international level. They also support researchers directly by hosting scientific conferences and public events, and by allocating funds to support research on aging.

DESCRIPTION

Longevity and life extension movements bring together people who believe that future technological developments will enable human beings to enjoy healthier and longer lives.

The members in these movements aim to educate the general public regarding the progress and potential of geroscience. Longevity movements often organize conferences, events and public debates about the future of aging. In this way, they attempt to change the zeitgeist by convincing others that life extension is not a distant dream. Several advocacy organizations have developed into niche media outlets, providing news of rejuvenation research in plain language, as well as coverage of relevant conferences.

Longevity movements usually advocate for funding to be directed toward anti-aging and age-reversal research and development efforts, both in the academy and the pharmaceutical industry.

Longevity movements also support research on aging directly by hosting scientific conferences, investment pitch meetings, and by allocating funding to research institutions and groups. In most cases these funds, whether donated directly or raised via crowdfunding, are allocated to support early-stage, high-risk research.

IMPORTANCE FOR OVERCOMING OBSTACLES

Longevity and life extension movements have the power to disseminate accurate information about longevity treatments, counter disinformation about such treatments and respond to certain ideological objections against life extension. They can also influence the zeitgeist by reminding the public, governments, and companies that healthy longevity and life extension are not necessarily a wild dream, but may actually be achieved in our lifetime. While their direct financial contribution to supporting studies on aging is small compared to governmental funding, they aim to focus their efforts where it is needed the most: studies to improve understanding of the mechanisms of aging, biomarkers, and to identify new drugs and therapies.

So far, the most successful national advocacy initiatives have helped to improve public policy and empower research programs related to aging and non-communicable diseases in several countries. Notable accomplishments include the addition of the special code "Aging-Related" into the WHO's International Classification of Diseases 11 (ICD011),[368] altering the WHO's policy

agenda to include a focus on the problems of the aging population,[369] and the inclusion of healthy life years as a metric to assess the productivity of the WHO's efforts at promoting health and wellbeing throughout the world.[370]

CURRENT STATUS AND USES

There are many movements dedicated to longevity throughout the world. While the list is too large to mention each by name, in 2013 longevity activists in more than 30 countries—including Belgium, India, Ireland, Australia, Israel, and Pakistan, to name a few—celebrated International Longevity Day around the world.[371]

In some countries, like Russia, longevity movements have also created political longevity parties, though they have not managed to actually get any members into congress.[372] In Israel, life extension activists approached politicians in a bid to establish a government agency to combat aging.[373] In the U.S., longevity activist and popular columnist Zoltan Istvan has run for the presidency advocating for longevity and life extension.[374] His campaign was designed to attract attention to the longevity movement and raise public awareness of their ideas and goals. In Germany, the German Party for Health Research was founded with the goal of increasing funding for aging research. In 2019, a representative of the party ran for European Parliament, and collected 71,000 votes, around one-third of the number needed to win a seat.[375]

The current stage of development of several longevity advocacy organizations and their partnerships is sophisticated enough to make significant gains like those previously mentioned.

CHALLENGES

Some longevity activists often rely on so-called radical messaging, pushing for controversial topics like immortality instead of promoting scientific research aimed at preventing, curing or reversing aging-related diseases. Such radical activists are generally viewed as eccentrics both by the public and government officials. These stereotypes make it difficult for them to influence the zeitgeist or effect concrete political change, whereas the organizations that are spreading softer messages do not tend to face similar resistance.

The negative perception is worsened by the fact that some longevity organizations also sell anti-aging supplements, whose efficacy is debatable. Many longevity activists nevertheless use these supplements and advocate for them with little reservation.[376]

Finally, longevity movements tend to suffer from limited funding, leading by necessity to limited actions.

Improving Science and Media Literacy

RELEVANT OBSTACLES

- Misinformation About Longevity Treatments
- Concern of Overpopulation Straining Earth's Resources
- Accessibility of Treatments
- Ideological Objections
- Social Perceptions of Aging and Biases Against Aging

SUMMARY

Science and media literacy are critical for stopping the spread and impact of misinformation, especially health-related. Someone with literacy in these fields can more easily distinguish between real, verified information and misinformation. Thus, pernicious forces limiting progress in longevity can be quashed at the individual level.

DESCRIPTION

Science-literacy is the understanding of scientific ideas and concepts, which allows a person to make well-informed and rational decisions. According to the National Association for Media Literacy Education, media literacy "empowers people to be critical thinkers and makers, effective communicators and active citizens."[377] In the absence of media and science literacy, false or misleading information is not only perpetuated, but can even become part of "conventional wisdom" and widely accepted as factual.

There is a clear need for prevalent and accessible science and media literacy training and education opportunities to help people better discern which sources are reputable, and to limit the spread of viral misinformation.

IMPORTANCE FOR OVERCOMING OBSTACLES

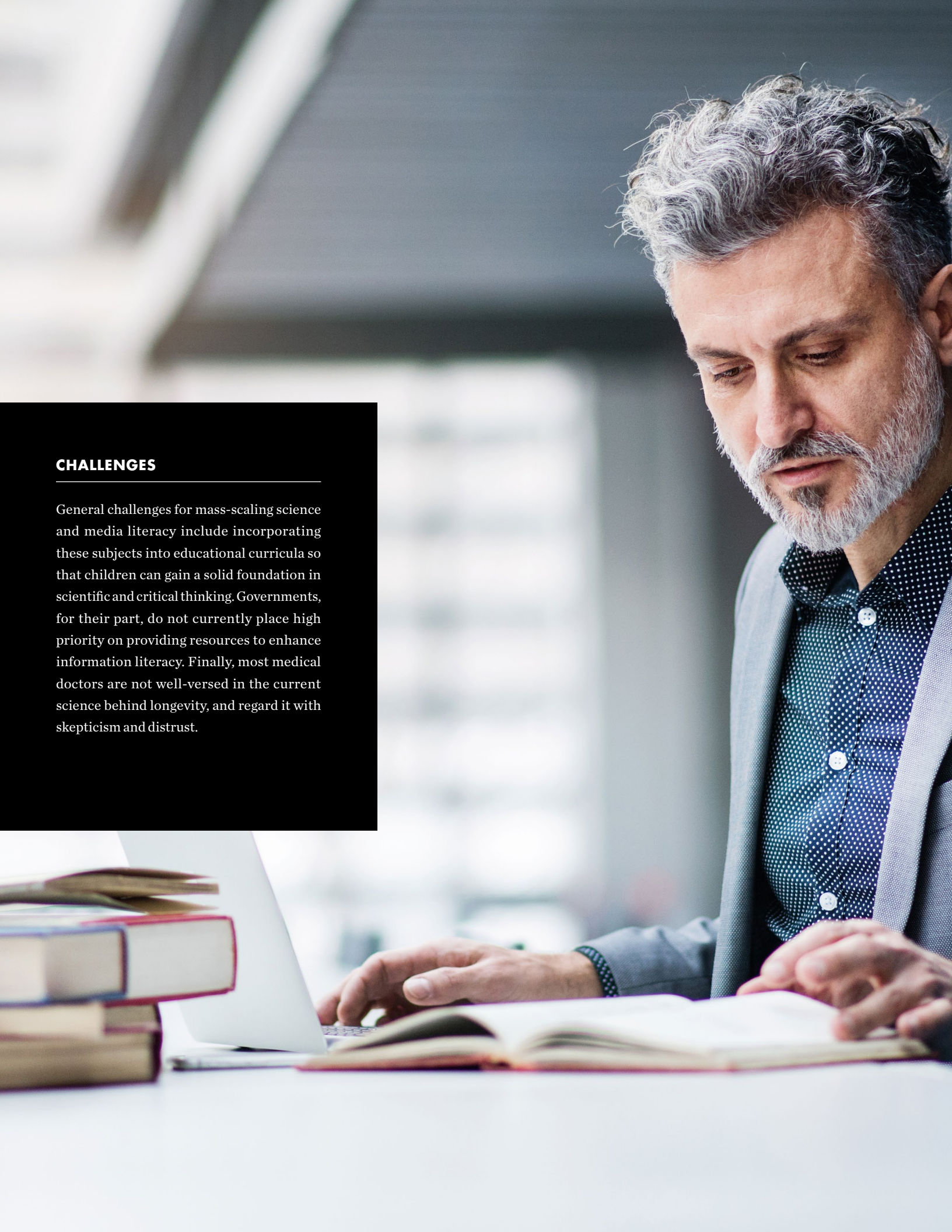
Science and media literacy are critical for stopping the creation of false or misleading information, and for reducing its reach and impact. Media-literate people can better decide which news pieces are reliable enough to accept as true and share with others. Similarly, people armed with science literacy can better understand whether a certain discovery merits the hype that may accompany it.

CURRENT STATUS AND USES

Virtually every school and university provides basic science literacy as part of the scientific education they offer to students. There are also many organizations dedicated to providing science literacy via specialized programs and competitions.[378] Similarly, there are several organizations and programs dedicated to enhancing media literacy.[379]

Still other organizations invest in promoting science literacy specifically in the field of longevity and life extension. Certain online science publications provide information about the latest developments in the biology of health and aging in a way that is compelling and digestible to the general public. These advocacy organizations serve as gatekeepers and resource providers to educate more people on the field's potential beyond what was previously perceived as pseudoscience. Some of the advocacy organizations also run workshops for longevity journalism to improve the quality of the content that the mass media produce.

Patient education programs can also improve science literacy. In such programs, people with a given health issue are provided with information about their disease/condition, modern treatment options, and how to use relevant interventions and diagnostic tools.[380] Certain national social advertisement campaigns are also intended to improve health literacy.



CHALLENGES

General challenges for mass-scaling science and media literacy include incorporating these subjects into educational curricula so that children can gain a solid foundation in scientific and critical thinking. Governments, for their part, do not currently place high priority on providing resources to enhance information literacy. Finally, most medical doctors are not well-versed in the current science behind longevity, and regard it with skepticism and distrust.

Reclassifying Aging Processes and Symptoms as a Treatable Condition

RELEVANT OBSTACLES

- Slow Pace of Drug Development and Approval
- Accessibility of Treatments
- Governments Don't Classify Aging as a Treatable Condition
- Social Perceptions of Aging and Biases Against Aging

SUMMARY

Reclassifying aging as a disease could help draw funding and efforts toward the development of age-reversal treatments. While the World Health Organization has recently recognized the existence of "aging-related diseases" in its International Classification of Diseases (ICD-11), other regulatory bodies have still to make a similar shift.

DESCRIPTION

There are currently efforts to classify the aging process and its aging-related symptoms as a treatable condition, or even as a disease. Several scientists have called for aging to be classified as a disease, arguing that it should be treated like many other diseases and medical conditions.[381]

IMPORTANCE FOR OVERCOMING OBSTACLES

Classifying aging as a disease would catalyze R&D efforts to develop age-reversal treatments, and accelerate existing efforts. It will encourage pharmaceutical firms to direct money toward such projects, making it more likely that age-reversal drugs would find their way to the market sooner rather than later. Furthermore, the reclassification of aging as a disease would allow medical doctors to administer treatments and medications that can help treat aging-related conditions and processes that up until now were largely ignored.

Finally, reclassification of aging as a disease has the potential to change the public view about aging, and could help people understand that there is a chance to escape the vicious cycle that nature has set for human beings.

CURRENT STATUS AND USES

In 2018, the World Health Organization (WHO) recognized the existence of "aging-related" diseases in its International Classification of Diseases codes (ICD-11). These diseases are described as "caused by pathological processes which persistently lead to the loss of the organism's adaptation and progress in older ages". The WHO's decision was made following a proposal submitted by a task force composed of researchers at the Biogerontology Research Foundation, the International Longevity Alliance, and the Council for Public Health and Demography. The task force, in turn, was consolidated following a call-to-action by Dr. Alex Zhavoronkov published in 2015.[382]

While the WHO's decision is not the same as acknowledging aging as a disease, it does make clear that aging is now being conceived of as a "major disease risk factor", as a Lancet editorial put it.[383]

Another development, from 2015, was not as official as the WHO's decision, but still suggests a movement toward the classification of aging as a disease. The FDA authorized a trial to test metformin, which has the potential to reduce the incidence rate of aging-related diseases and conditions. In effect, the drug could be considered a promising longevity treatment, giving the sense that the FDA is moving closer towards classifying aging as a disease.[384]

CHALLENGES

The fact that there is no agreement about the exact set of aging biomarkers that could be used to measure aging makes it difficult for aging to be identified as a concrete and easily identifiable disease. On the social front, there is a concern that many people would feel uncomfortable at the realization that they are essentially the carriers of a deadly disease—especially while there is no cure for that disease as yet.

Finally, to pass new laws on this issue, several stakeholders—the pharmaceutical industry, scientists, older adults organizations and the regulator—must join forces. Such collaboration, however, may not be easy to achieve.

DIY Medicine

RELEVANT OBSTACLES

- Misinformation About Longevity Treatments
- Slow Pace of Drug Development and Approval
- Accessibility of Treatments
- Governments Don't Classify Aging as a Disease

SUMMARY

So-called biohackers can conduct their own research on drugs, and even manufacture existing drugs in their homes—or teach others how to do so easily with widely-available tools. Biohackers thus may develop longevity treatments alongside the established pharma industry, as well as anecdotally demonstrate their effectiveness—sometimes on their own bodies.

DESCRIPTION

Do-It-Yourself (DIY) is a method and ethos that can apply to a broad range of disciplines. It champions a process of creation, modification, and/or experimentation without the direct involvement of putative experts. DIY is commonly associated with arts, crafts, and electronics, though some "makers" (people who pride themselves on leading the DIY revolution) also dabble in biotechnology as "biohackers".

The tools for DIY medicine today include kits for genetic engineering (such as small and inexpensive PCR devices and CRISPR-Cas9 kits), home devices for synthesizing chemicals and drugs, easy-to-use sterilization devices (often simply pressure cookers), and 3D printers to manufacture new parts for such kits. All these can usually be purchased online.[385]

IMPORTANCE FOR OVERCOMING OBSTACLES

Biohackers, by conducting DIY medicine, can help accelerate drug development and approval in several ways:

- Biohackers often experiment on their own bodies and even organize patient-driven pilot clinical trials on humans, thus providing anecdotal demonstration of the efficacy and safety of new drug candidates.[386]
- Biohackers can manufacture medicine and drug candidates in their homes, and distribute them free-of-charge to the masses.[387] The public can thus get access to drugs that are currently being tested.
- In the future, biohackers could compete with more established pharma firms, forcing them to innovate and optimize their drug testing process. Should alternative drug testing processes utilized by biohackers prove superior to those required by the regulator, governmental authorities will be compelled to similarly revamp the current drug approval process.

Biohackers wielding self-designed tools could manufacture drugs in their homes and sell them to the public. Even though this practice is forbidden by law, it is not clear whether the authorities will be able to stop it easily or completely. In this way, biohackers and DIY medicine could also help make age-reversal drugs more accessible. This possibility also means that even if governments fail to characterize certain aspects of aging as a treatable disease, biohackers could make sure that the drugs needed to treat aging will reach those who need and want them.

CURRENT STATUS AND USES

According to the DIYbiosphere website, there are currently 29 biohacking groups, 56 biohacking labs and at least eight biohacking incubators.[388] It is likely that the actual numbers are significantly larger.

Some of the best-known biohacking organizations include:

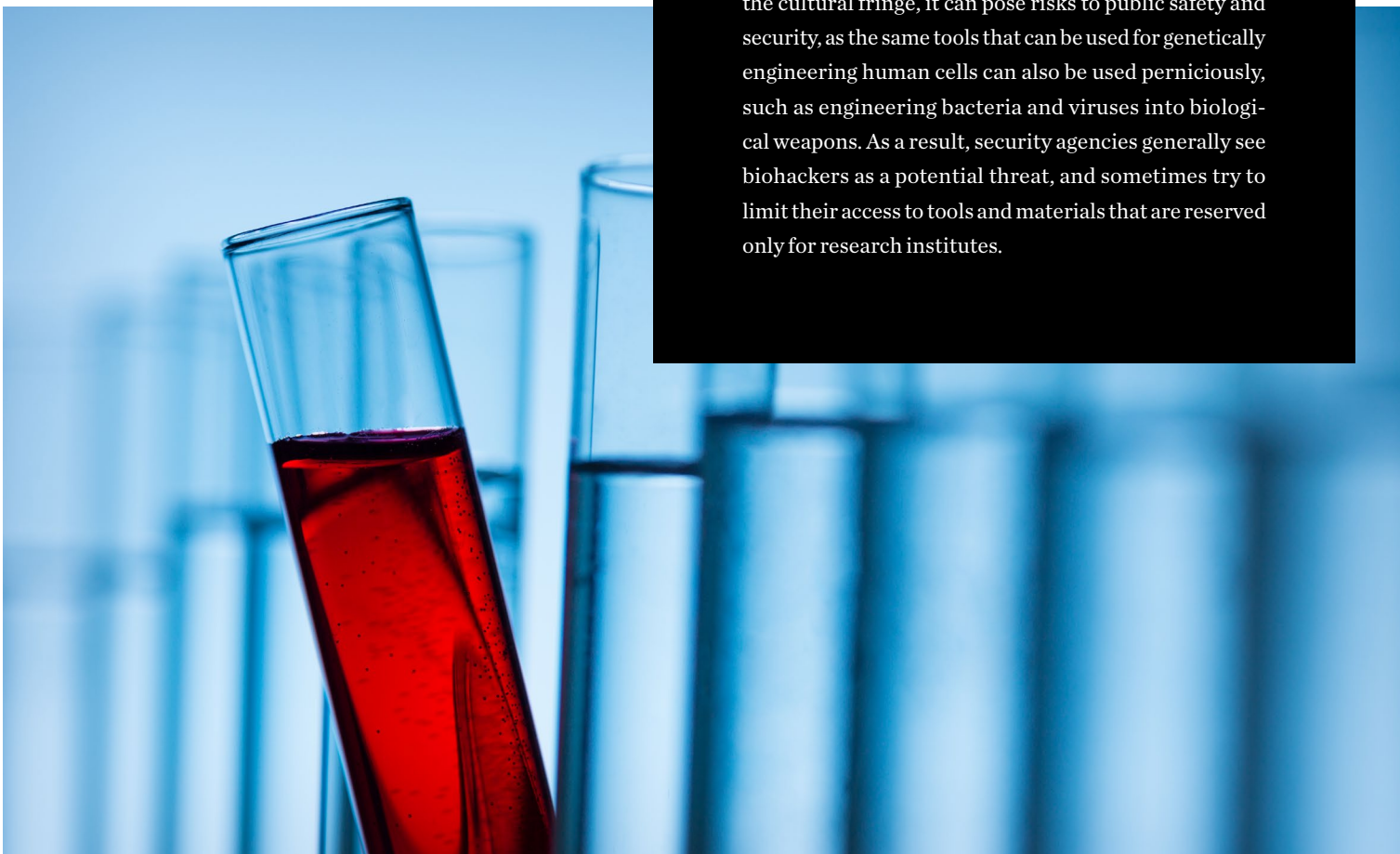
» **iGEM:** An annual biohacking competition, in which the competitors—ranging in age from high school kids to grad students—invent new molecular machines, design and hack cellular genetic circuits, and acquire state-of-the-art tools for the purposes of genetic engineering and molecular biotechnology work.[389]

» **The Four Thieves Vinegar Collective:** This collective is a group of volunteers who develop DIY medical tools and technologies, including tiny home-based chemical plants for producing new drugs. The group has used these devices to manufacture naloxone (which prevents opiate overdoses), daraprim (a drug for alleviating infections in HIV carriers), cabotegravir (HIV medicine), mifepristone and misoprostol (abortion-inducing drugs).[390]

CHALLENGES

DIY-made drugs carry inherent risks for the users, since their manufacturing process is almost always unregulated, and the end products may be contaminated. In addition, biohackers often suffer from negative public relations, and are perceived as reckless and impulsive, since many of them experiment on their own bodies. This means that even if meaningful insights could be gleaned from DIY experiments, it will be difficult for the industry, regulators and the public to treat them seriously as their results will be largely anecdotal and lack adequate sample size.

Lastly, as long as DIY medicine remains a practice on the cultural fringe, it can pose risks to public safety and security, as the same tools that can be used for genetically engineering human cells can also be used perniciously, such as engineering bacteria and viruses into biological weapons. As a result, security agencies generally see biohackers as a potential threat, and sometimes try to limit their access to tools and materials that are reserved only for research institutes.



Artificial Intelligence for Drug Development

RELEVANT OBSTACLES

» Misinformation About Longevity Treatments

» Slow Pace of Drug Development and Approval

» Accessibility of Treatments

» No Set of Agreed-Upon Biomarkers for Quantifying Biological Age

SUMMARY

Artificial Intelligence (AI), leveraging increasingly abundant data, can accelerate the development of safe and effective aging treatments in numerous ways.

DESCRIPTION

Through its superhuman ability to analyze large amounts of data and find relevant patterns and connections, Artificial Intelligence can theoretically expedite virtually every stage of the drug development process. As Zhavoronkov and colleagues discuss in Artificial Intelligence for Aging and Longevity Research[391] and others note elsewhere, applications of AI for speeding up drug development include:

» Gaining novel insights about diseases to inform new hypotheses for drug discovery

» Identifying new targets for therapeutics

» Accelerating the development of molecular compounds used for treatment

» Developing biomarkers of aging

» Discovering new purposes for existing drugs (which have already been deemed safe)

» Testing safety and efficacy of drugs through trial simulations[392]

» Improving inclusion/exclusion criteria for identifying and screening trial participants[393]

» Running pre-trial simulations to inform whether a full-on clinical trial design should be pursued or altered[394]

» Developing chatbots to help people enroll in trials[395]

» Informing trial design decisions to increase the likelihood of success[396]

» Supporting post-trial analysis of drug safety and efficacy by analyzing real-world data[397]

» Using personal data (e.g., from a digital avatar) to design and prescribe precision medicine[398,399,400]

IMPORTANCE FOR OVERCOMING OBSTACLES

Some argue that the use of data has been the primary force behind progress in medicine. Humanity now has the capacity like never before to collect, store, and organize data, with the volume of data increasing exponentially by the year. This is especially relevant given the increasing facility to use artificial neural networks that use massive swathes of data to obtain new insights. As illustrated by the above examples, these insights can ultimately reduce the time and money needed to demonstrate a treatment's safety and efficacy. They can also ensure that even personalized treatments—the kind that require expert work to adapt the treatment to the patient—can be mass-scaled.

CURRENT STATUS AND USES

Several drug R&D companies have begun using AI, particularly machine learning and predictive analytics. Examples include big

pharmaceuitcal companies Pfizer, Roche, and Novartis[401] [402] and a variety of other companies including:

- NuMedii (founded 2008)
- Atomwise (2012)
- Exscientia (2012)
- BenevolentAI (2013)
- Cyclica (2013)
- Insilico Medicine (2014)
- Bioage (2015)

Despite the clear potential, some criticism has been levied that AI's promise in healthcare has been overhyped and its performance has thus far under-delivered.[403] [404] Efforts are ongoing to optimize analytical frameworks and architectures.[405]

CHALLENGES

Since data is the fuel on which AI runs, the more it is standardized across organizations, sectors, and countries, the more valuable and deployable the insights.[406] A great deal of data that is useful for AI, however, comes from human subjects, and thus common concerns about data privacy and security may slow progress.[407] Additionally, lack of trust in AI may limit acceptance of the evidence of safety and efficacy derived from it. Finally, concerns about AI perpetuating human prejudices are well documented.[408] [409] Using AI for drug development must account for an overrepresentation of well-researched drugs, diseases, genes and even population groups, which could limit the technology's ability to uncover novel insights and drive new, faster decision-making. [410]

> "AI has great potential to accelerate preclinical progress in the field in several ways. Identification of candidate interventions and biomarkers are just a couple. The bigger challenge still remains how do you test and validate these things in people."

DR. MATTHEW KAEBERLEIN
BIOGERONTOLOGIST

Promoting and Embracing a Multi-Stage Life

RELEVANT OBSTACLES

» Accessibility of Treatments

» Governments Will Face Difficulties with Current Pension Laws

» Ideological Objections

» Social Perceptions of Aging and Biases Against Aging

SUMMARY

In contrast to the entrenched lifetime sequence of education, career, retirement, a multi-stage life champions a fluid and flexible integration of learning, working, and resting throughout one's life. Widespread embrace of this outlook would help to mitigate the problems associated with the current ratio of working-population to entitlement-recipients.

DESCRIPTION

As healthspan increases, the traditional life paradigm of going to school during youth, working during adulthood, and being retired during one's twilight years may become increasingly outdated, impractical, and undesirable. With more years of life, people's demands, expectations, and motivations will change.[411] In response, a multi-stage life paradigm upends the entrenched three-stage life of learn, work, rest, and replaces it with a more fluid, lifelong integration of these activities. Each activity may occur at different periods throughout one's long and vital life in accordance with one's evolving interests and priorities.

Companies, governments, and individuals all have a role to play in bringing about a world where a multi-stage approach to life is the norm.

Lynda Gratton and Andrew Scott have written extensively on what *companies* can do to accelerate a working world that embraces a multi-stage life.[412] Their suggestions include:

» Rethinking age-related stereotypes and ending the association of one's age with one's career stage and the associated benefits and responsibilities

» Prioritizing the "intangible assets" they offer their employees, that is, assets that facilitate a nimble life, rather than focusing on financial assets; intangible assets include the opportunity to build skills and knowledge, strengthening one's network, and having a healthy work-life balance

» Revamping HR recruitment and retention strategies to align with the evolving interests and experience levels of prospective employees, and seeking out skills like adaptiveness and flexibility that will be needed for the future of work[413]

» Bringing variety to the employee experience

» Acknowledging and accommodating the needs of dual-career families

» Creating time flexibility

Others discuss adapting workplace dynamics to give people more autonomy on how, where, and when they work;[414] incorporating new levels of employment, like a "returnship" for someone returning to the workforce after extended time-off; and writing formal policies for how employees can and should incorporate other priorities, such as side businesses, professional development, or personal hobbies.[415] Finally, incentivizing physical activity and healthy eating at work can be also help reduce healthcare costs and increase productivity.

CHALLENGES

Whereas workers may desire more personalization and flexibility from their employers, companies may continue to strive for standardization and conformity. What's more, conflicting interests based on one's age bracket hamper political will to make policy changes. The elderly usually favor the status quo of retirement and healthcare benefits, whereas the young are more in favor of changes to promote lifelong education and skills development, flexible working policies, and a friendlier attitude to life transitions.

Actions that *governments* can take include social advertisement campaigns, reducing taxes for health-promoting businesses, changing laws to shift vacation and sabbatical allowances, providing tax breaks for continued education,[416] preparing children in school to adapt to a multi-stage life,[417] and more strictly eliminating age as a factor in hiring, promoting, and firing decisions.[418]

As for *individuals*, attitudinal shifts are already manifest in the growth of the gig economy and the number of digital nomads. To prepare for a life where an undergraduate degree may be earned at 20 or 60 years, and where a manager may be 70 or 30, some experts suggest focusing on cultivating emotional intelligence, committing to lifelong learning, and understanding how to be nimble.[419]

IMPORTANCE FOR OVERCOMING OBSTACLES

A multi-stage life eschews the assumption that people will retire at 65—or even that they will retire at all. By embracing and enabling this lifestyle, society will be much more capable of supporting the massive demographic shifts that will accompany a longevity revolution.

CURRENT STATUS AND USES

Some employment practices are in use by varying degrees. Of all freelancers over 55, nearly 50% are taking part in gig work and the gig economy.[420] The proportion of U.S. workers taking part in the gig economy rose from 10% to nearly 16% between 2005 and 2015.[421] Digital nomadism is similarly on the rise, with 4.8 million American workers referring to themselves as digital nomads, and 17 million more aspiring to join them in the future.[422]

Despite the rise in numbers of digital nomads and gig workers, it is clear that at present the massive scale-up of this attitudinal and cultural shift remains a distant vision.

Retirement Reform

RELEVANT OBSTACLES

» Concern of Overpopulation Straining Earth's Resources

» Governments Will Face Difficulties with Current Pension Laws

» Social Perceptions of Aging and Biases Against Aging

SUMMARY

Reforming retirement systems can help increase the sustainability of public and private age-dependent benefits by increasing the number of working older adults.

DESCRIPTION

Broadly speaking, there are two methods for reforming the retirement system to respond to the looming fiscal imbalance crisis: [1] changing the retirement age or [2] implementing a so-called flexible retirement policy.

As for changing the retirement age, there are two age-related milestones that may be subject to such a shift: the normal retirement age (NRA) and the early retirement age (ERA). NRA is the age at which someone is eligible to receive full retirement benefits. ERA is the age at which someone is eligible to receive partial retirement benefits. ERA may apply to benefits received from the public and private sectors at different times; for example, in the US today, social security ERA is 62, while 59.5 is the age at which one can withdraw from an individual retirement account (IRA) without penalty (with some exceptions allowing for penalty-free withdrawal at age 55).[423]

Several studies have found that raising the NRA and/or ERA generally improves the so-called dependency ratio, that is, the ratio of people not in the labor market to people working, based on age (i.e., usually calculated as the ratio of under-14 plus over-65 to 15-65 year olds). Research has also shown, however, that doing so may have unintended consequences, including negatively impacting workers in poor health, with less desirable skills, and some older workers.[424,425] Significantly, raising the retirement age is widely considered politically fraught and a "third rail" that legislators are wary of touching.

A flexible retirement policy is more politically attractive than raising the retirement age. There are various versions of flexible retirement, but the common idea is that as workers age they gradually reduce their time spent working and gradually increase the benefits they receive. One 2018 study looking at empirical data from nine OECD countries with flexible retirement policies found, however, that the policy fails to increase the labor supply of older workers, and may even reduce it.[426] The authors explain this is because the increase in labor supply is equaled or in some cases outweighed by the decrease in total hours worked. They suggest that raising the retirement age should not be considered problematic since the extension in life expectancy allows for the ratio of years worked-to-years in retirement to remain unchanged—and they support a policy that would automatically adjust the retirement age over time in order to maintain this ratio.

IMPORTANCE FOR OVERCOMING OBSTACLES

Assuming that it is indeed a goal to preserve pensions in countries facing a dependency ratio crisis, reforming retirement to increase the labor force is one of only a few options to avoid fiscal insolvency. Other possibilities include generating more revenue to cover the growing liabilities (e.g., by increasing the contributions made by workers or through taxation) or finding new ways to increase the labor force (e.g., by increasing female employment).[427,428] It is also possible that people will voluntarily work later into their (healthier) lives, thereby increasing the effective retirement age and helping to at least delay the crisis without the need to enact legislation.

CURRENT STATUS AND USES

It is beyond the scope of this report to discuss every country's retirement policy platform, but a review of relevant literature suggests that change is afoot. As the Finnish Centre for Pensions has noted, many countries in Europe have scheduled changes to the retirement age, set to take effect between 2020-2030. Most of these increases are in the 2-3 year range. Some of these countries will or already do link retirement age to life expectancy.[429] Japan is reportedly considering allowing pensioners to begin drawing their funds after the age of 70,[430] though this would be an optional rather than a mandatory threshold. The U.S. has a planned, gradual increase in retirement age up to 67, set to take effect in 2027.[431] China is struggling to implement retirement reforms that rely on a taxation overhaul,[432] while in 2017 India raised its retirement age limit to 65.[433]

Although such plans give reason for optimism, they are also subject to political will, and the decisions for increases can be reversed. Indeed, politicians have scaled back plans for increasing the retirement age in Russia and Australia, among other places.[434,435]

CHALLENGES

Reforming retirement is a political challenge, whether the reform is through altering the retirement age or finding new ways to raise revenue. These tend to impose immediate costs in exchange for longer-term benefits, which is usually not an optimal scenario for politicians who wish to be re-elected. Similarly, the fact that older people (who tend to vote more) will have to bear the most immediate losses makes this a tough issue for politicians to manage.

Governments Promote Generic Drugs

RELEVANT OBSTACLES

» Misinformation About Longevity Treatments

» Slow Pace of Drug Development and Approval

» Accessibility of Treatments

SUMMARY

By cautiously expanding the availability of generic drugs and ensuring a level of competition in the generic drug market, governments can provide greater access to affordable treatments.

DESCRIPTION

Generic drugs use the same active ingredients as the name-brand version and thus for the most part have the same benefits and risks. Since the upfront cost for demonstrating their safety and efficacy is significantly reduced, generic drugs tend to be cheaper and therefore more accessible than name-brands. Generally, generic versions receive regulatory approval only after the patent of the name-brand version expires. Additionally, when multiple applications for a generic drug are approved, market competition usually drives down prices.[436,437] Generic drugs can also be a means for repurposing old name-brand drugs with expired patents as a new treatment for diseases other than their original target.[438] Access to generic drugs has been shown to improve the patient experience of Medicare recipients.[439]

Increasing awareness of the value and safety of generic drugs would likely make an impact, as a lack of trust and lack of knowledge have been identified as common causes of the lack of uptake of generic drugs.[440,441]

IMPORTANCE FOR OVERCOMING OBSTACLES

Cost of drugs plays an essential role in the accessibility of treatments, and the prioritization of generic drugs can help reduce prices for consumers. Given that such prioritization can dissuade the pharma industry from researching new and innovative drugs, however, this remedy must be exercised thoughtfully and prudently.

CURRENT STATUS AND USES

Although the U.S. FDA allows for an expedited approval pathway for certain generic drugs,[442] there are several other levers the public sector could pull to further facilitate the proliferation of generics. These include allowing more organizations to market generic drugs, increasing funding for promoting the generic drug market, and exercising legal rights to intervene in pricing for drugs that it has helped to fund.[443,444] 2020 Democratic presidential candidate Elizabeth Warren has proposed creating a federal Office of Drug Manufacturing for the purposes of producing generic drugs. Bernie Sanders, another presidential candidate, has a proposal to achieve affordable generics through license-granting system.[445]

The private sector can also play a role in increasing the prevalence of generics. Pharmacy benefit managers and pharmaceutical companies, for example, could adopt purchasing and pricing mechanisms based on patient outcomes rather than profit margins, which could increase the supply of generic drugs.[446] Even the way physicians refer to drugs—that is, by using generic names instead of brand names—may aid the proliferation of generic drugs.[447]

CHALLENGES

Though generally considered safe, there are some concerns with the safety of generic drugs, especially those whose supply chains are in developing countries, where regulatory standards tend to be more lax.[448,449] Generic drugs also often suffer from negative stigma, while name-brand drugs enjoy good publicity. Prioritization of generic drugs will require influencing public perception, as well as overcoming the fear that distorting the incentive mechanisms of drug research and development will limit innovation. [450,451]

It will also require persuading doctors, health services, and insurers to change their practices, however, such coordination is likely to be difficult to achieve. [452]

Regulations to Facilitate Competition in the Pharmaceutical Market

RELEVANT OBSTACLES

» Misinformation About Longevity Treatments

» Slow Pace of Drug Development and Approval

» Accessibility of Treatments

SUMMARY

Governments can choose to alter or even ignore existing patent laws—whether in correspondence with international law or not—and thus cheaply manufacture existing prescription drugs in their territories. Several countries—Thailand, Brazil, Germany—have taken this approach before, with varying success.

DESCRIPTION

The high price of prescription drugs limits their availability, but this issue can be mitigated or even circumvented through the aid of government regulation. In the U.S. system, the prices for the world's top-selling prescription drugs are on average three times higher in the U.S. than in Britain.[453] Some researchers argue that such phenomena are symptoms of certain regulatory decisions,[454] including:

» The U.S. government allows drug manufacturers to set their own prices, unlike most other places in the world. A now infamous and extreme example of this is the astronomical price raising of Daraprim—an anti-malaria and anti-HIV drug—from $13.50 a tablet to $750.[455]

» The U.S. government reserves the right to allow pharmaceutical companies to maintain a long-term monopoly over the manufacturing and selling of certain name-brand drugs.

» Some U.S. state laws hinder the ability of generic drug manufacturers to lower drug costs. In many states, for example, pharmacists are required to get patient consent in order to purchase a generic drug. This friction often leaves generic drugs untapped.

One potential remedy to these issues is deceptively simple: since governments enjoy a territorial monopoly, they can —at least in theory—override patent laws if deemed necessary. Governments can do this by issuing compulsory licenses of pharmaceutical patents, which would allow other firms in the country to compete in manufacturing and selling the patented drugs—while paying the original developer of the drug a modest fee.[456]

Other possible solutions include setting a price range for certain drugs, removing laws that obstruct generic drug use (such as the one described above), making drug manufacturers compete on prices (in accordance with the so-called "Kiwi model"),[457] and shortening the monopoly time alloted in patent laws. These approaches can facilitate better competition in the drug market and help to lower drug costs. Such legal tools, however, should be wielded with extreme caution, since they also have the potential to discourage innovation and investment among both incumbents and startups.

IMPORTANCE FOR OVERCOMING OBSTACLES

In a private market, accessibility of medical treatments is mostly determined by prices and insurance coverage. Governments can intervene, however, to reduce drug prices, but they must do so with care.

CURRENT STATUS AND USES

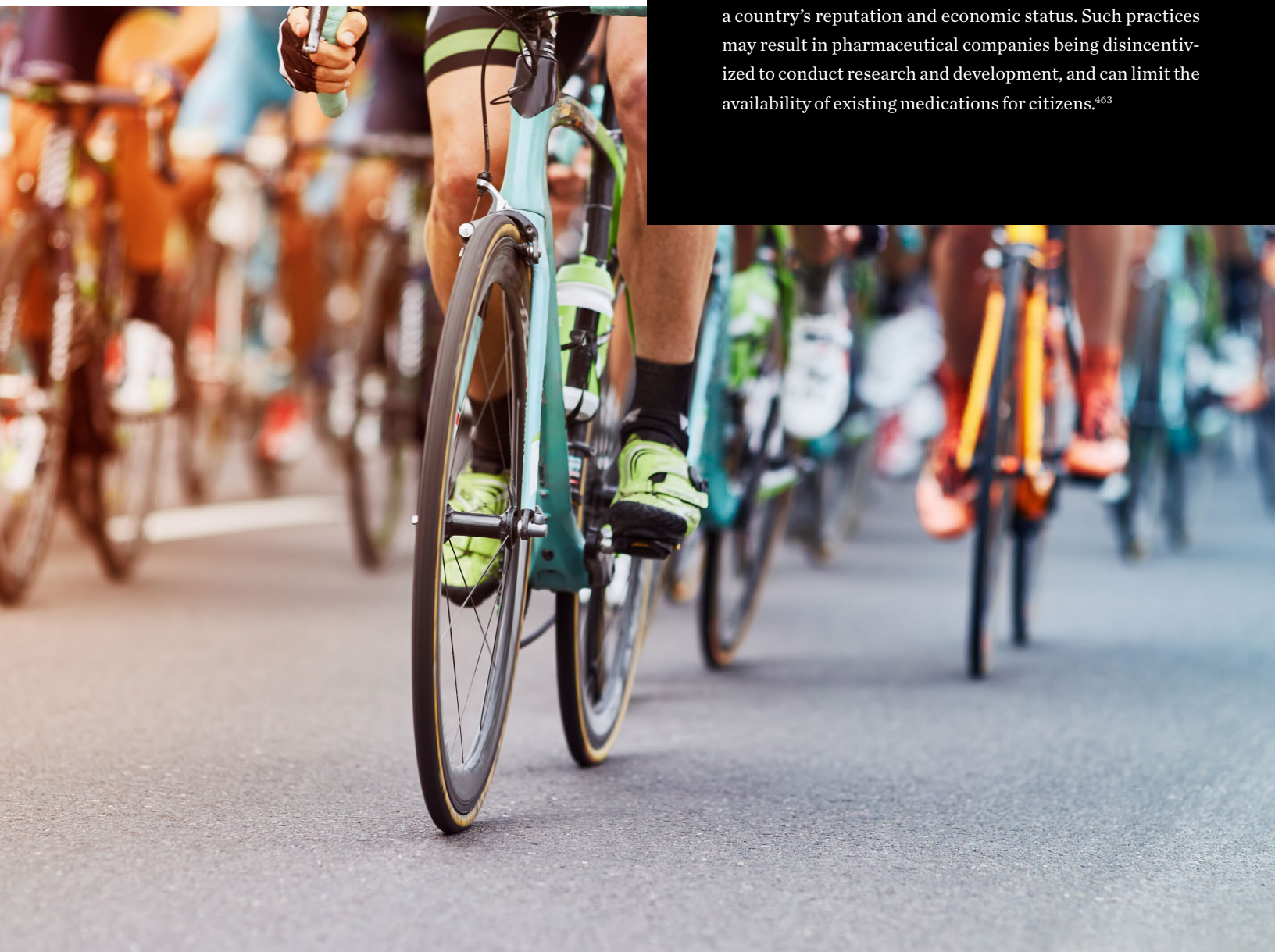
Both Thailand and Brazil issued compulsory licenses in 2007 for drugs used to treat AIDS and heart disease. While the World Trade Organization explicitly allows governments to issue compulsory licenses, such practices are expected to be reserved for public health crises. While the legality of these decisions has

been disputed, the end result is clear: both Thailand and Brazil managed to supply their citizens with the desired medication at extremely low prices.[458,459] According to reports on Fox News, former U.S. president Bill Clinton supported these moves.[460]

In 2012, meanwhile, India granted its first compulsory license to a domestic generic drug manufacturer to produce an anti-cancer drug.[461] In 2017, Germany followed in Thailand, Brazil and India's footsteps by issuing its first compulsory license for raltegravir, an antiviral compound used for treating AIDS.[462]

CHALLENGES

While governments can do things like issue compulsory licenses in their territories, such actions can negatively impact a country's reputation and economic status. Such practices may result in pharmaceutical companies being disincentivized to conduct research and development, and can limit the availability of existing medications for citizens.[463]



Universal Adherence to Common Data Standards

RELEVANT OBSTACLES

» Misinformation About Longevity Treatments

» Slow Pace of Drug Development and Approval

» No Set of Agreed-Upon Biomarkers for Quantifying Biological Age

SUMMARY

Adherence to common standards for structuring, defining, formatting, and exchanging data would expedite drug development by streamlining the use of existing and emerging health technologies and enabling greater collaboration across organizations, sectors, and geographies.

DESCRIPTION

Adherence to certain universal data standards could improve the speed and efficiency of drug development. Kush and Damji[464] provide several examples for how data standards could improve the drug development process. These include:

» Facilitating the collection and interpretation of data from clinical and research studies by both study sponsors and regulators

» Enabling the consolidation of data from disparate sources, thereby enhancing the insights that can be drawn and informing the design and planning of future research

» Expediting regulatory review by reducing or eliminating the need to clean, harmonize, scrutinize, and/or re-enter data

» Expanding the value of so-called real world data (e.g., from quantified-self applications) by making it more accessible and actionable

» Enhancing collaboration among different stakeholders

The value of data standardization is not lost on the U.S. Food & Drug Administration, the principal regulatory body of the United States. As the agency itself notes, by allowing regulatory reviewers to focus on the content of data rather than their form and structure, and by streamlining the integration of health data from multiple sources (including "electronic health records, insurance claims, mobile health, and even social media"), data standards have "the potential to make drug development and safety monitoring more efficient and faster."[465]

A study conducted by the Clinical Data Interchange Standards Consortium (CDISC) concluded that the pharmaceuitcal industry could reduce 70-90% of the time and resources currently spent on clinical research by adopting shared standards.[466]

Additional benefits of data standards include:

» Discouraging data silos[467]

» Facilitating international cooperation[468]

» Improving clinical trials' likelihood of success[469]

» Enhancing the value of artificial intelligence[470]

» Streamlining personalized medicine [471]

IMPORTANCE FOR OVERCOMING OBSTACLES

As the CDISC data cited above suggests, universal adherence to common data standards has enormous potential. In their 2018 Longevity Industry Landscape Overview, Deep Knowledge Analytics wrote that "acceleration of biomedicine has been mainly spurred by advances in collection, gathering, and analysis of data."[472] Universal data standards would help in all of these areas.

CURRENT STATUS AND USES

The FDA has a Data Standards Council with the goal of ensuring standardization across its agency.[473] There are numerous other organizations that aim to provide health data standards. These standards include:

- Clinical Data Interchange Standards Consortium (CDISC)[474]
- Digital Imaging and Communications in Medicine (DICOM)[475]
- Health Level Seven International (HL7)[476]
- Integrating the Healthcare Enterprise (IHE)[477]
- International Organization for Standardization (ISO)[478]
- Logical Observation Identifiers Names and Codes (LOINC)[479]
- Medical Dictionary for Regulatory Activities (MedDRA)[480]
- Systematized Nomenclature of Medicine (SNOMED)[481]

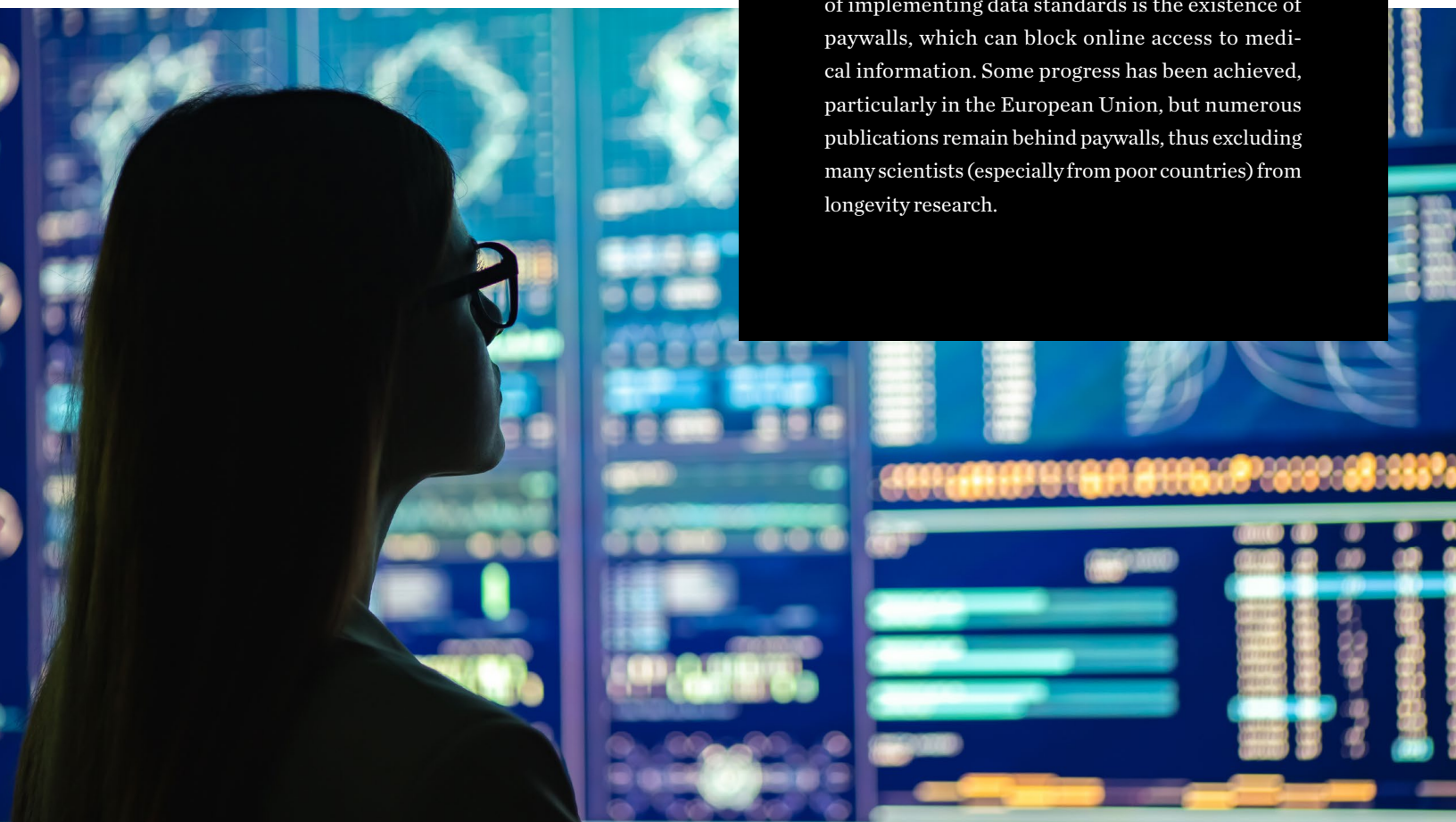
Blockchain could play a role in health data standards going forward. One UCLA study recently concluded a proof-of-concept for using blockchain to ensure clinical trial data integrity.[482]

CHALLENGES

The volume of worldwide data is enormous. Thus, while the impact of improved standardization would be high, so too are the hurdles to achieving it. One need only note how many "standards" already exist (the above list is far from comprehensive) to gather how challenging it is to achieve the level of coordination and compliance necessary to level-up the field. Furthermore, concerns and regulations around data privacy, such as HIPAA, create friction against streamlined standardization.

Another challenge relates to the competitive advantage that proprietary data offers in the free market. This disincentivizes collaboration and compliance. Benefits of time and cost savings associated with adherence to data standards would only come after an upfront cost associated with aligning data practices with the standards. The longer-run benefits thus must compete with the immediate costs.

One important factor that can affect the results of implementing data standards is the existence of paywalls, which can block online access to medical information. Some progress has been achieved, particularly in the European Union, but numerous publications remain behind paywalls, thus excluding many scientists (especially from poor countries) from longevity research.



Regulations to Expedite the Clinical Trial Process

RELEVANT OBSTACLES

» Slow Pace of Drug Development and Approval

» Accessibility of Treatments

SUMMARY

Governments can implement several regulatory changes to the drug approval process in order to significantly expedite it. These changes include expedited approval programs, promoting the use of in-silico clinical trials, prioritizing repurposed drugs, and others.

DESCRIPTION

There are numerous levers that governments can pull to speed up the approval process for longevity treatments. Some possibilities include:

» Placing certain treatments into expedited approval programs[483,484]

» Expanding the use of non-clinical trial data for making regulatory decisions (the FDA's Real World Evidence program, for example)[485]

» Championing cross-sectoral and international data standards to improve the use of non-clinical trial data for making regulatory decisions and increase public trust about data safety and security

» Incorporating statistical modeling into drug safety and efficacy determinations[486]

» Allowing clinical trials to modify their design midway through the study[487]

» Accommodating the use of organs-on-a-chip and organoids to reduce the burden of recruiting and retaining clinical trial participants[488]

» Prioritizing repurposed drugs, which have already been certified as safe[489]

» Pushing for the incorporation of in-silico clinical trials in the drug approval process[490]

» Promoting clinical trials among the old, oldest old and terminally-ill by implementing the right to take part in these trials on a case-by-case basis

» Abolishing the very expensive and time-consuming phase 3 clinical trials to shorten the duration of the drug-approval process (i.e., granting drug approval after only phase 1 and 2 trials)

» Creating a worldwide alternative to the FDA and EMA that works much faster and more efficiently, allowing for a more rapid drug approval

IMPORTANCE FOR OVERCOMING OBSTACLES

Regulators dictate the pace at which new drugs become available to consumers. While the regulator's purpose is a noble one—to prevent harm from medications that were not tested well enough—it might also be possible to lower the high standards set for new medications today, or at least to streamline the testing process. Should governments require pharma firms to utilize new and more rapid mechanisms for testing new treatments, the industry would certainly follow suit.

CURRENT STATUS AND USES

Currently the FDA has four expedited approval programs, each of which allows for various actions to be taken with the goal of speeding up the approval process. These appear to be making incremental, not exponential, progress.[491,492] The European Medicines Agency, Canada, and China offer additional examples of selective expedited drug approval programs, but data demonstrating efficacy of such programs is scarce.[493,494,495]

The FDA has recently published new guidelines on its real-world evidence program, which seeks to leverage non-clinical trial data to contribute to and presumably expedite the drug approval process. This framework is still in its early phases, and the FDA acknowledges that several hurdles still need to be addressed in order to unlock the benefits of real-world data. These hurdles include developing common data standards to provide information technology and scientific tools with consistent data, designing best practices for incorporating and assessing the reliability and relevance of data from a variety of sources (e.g., electronic health records, other countries, patient registries), and exploring strategies to integrate data from mobile technologies and quantified-self tools.[496]

Adaptive trial designs, which allow for mid-trial design modification, have been used for over 25 years but are not well established in practice. This may be due, at least in part, to a lack of familiarity with the processes and frameworks that are needed to ensure findings remain valid and relevant despite a mid-trial adjustment.[497]

As for using labs- and organs-on-a-chip to complement the use of real organs and expedite testing, although the FDA has funded external projects that look at bionic organs[498,499,500] and is funding research into "organs-on-chips" technology,[501] there does not appear to be any evidence of current use of synthetic body parts to expedite regulatory testing.

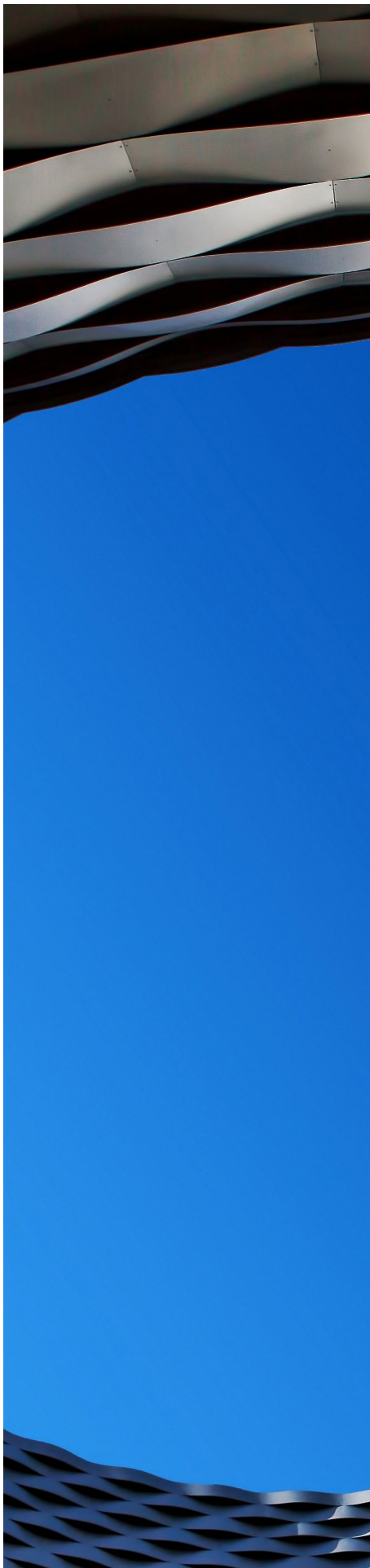
CHALLENGES

Expediting the drug approval process could be construed, rightly or wrongly, as a lowering of safety standards, potentially causing a public uproar. Furthermore, high standards for drug approval tend to necessitate a large capital investment to introduce new drugs to the market, thus creating an industry of big firms. Large pharma firms may lobby lawmakers to prevent change to the field that could upend their entrenched advantages.

Finally, there's always the fact that we do not yet fully understand the workings of the body. While in-silico clinical trials (essentially computer simulations of cells and tissues) are starting to be utilized, we can't (yet) create models accurate enough to replace testing on animals and/or human beings.

Conclusion

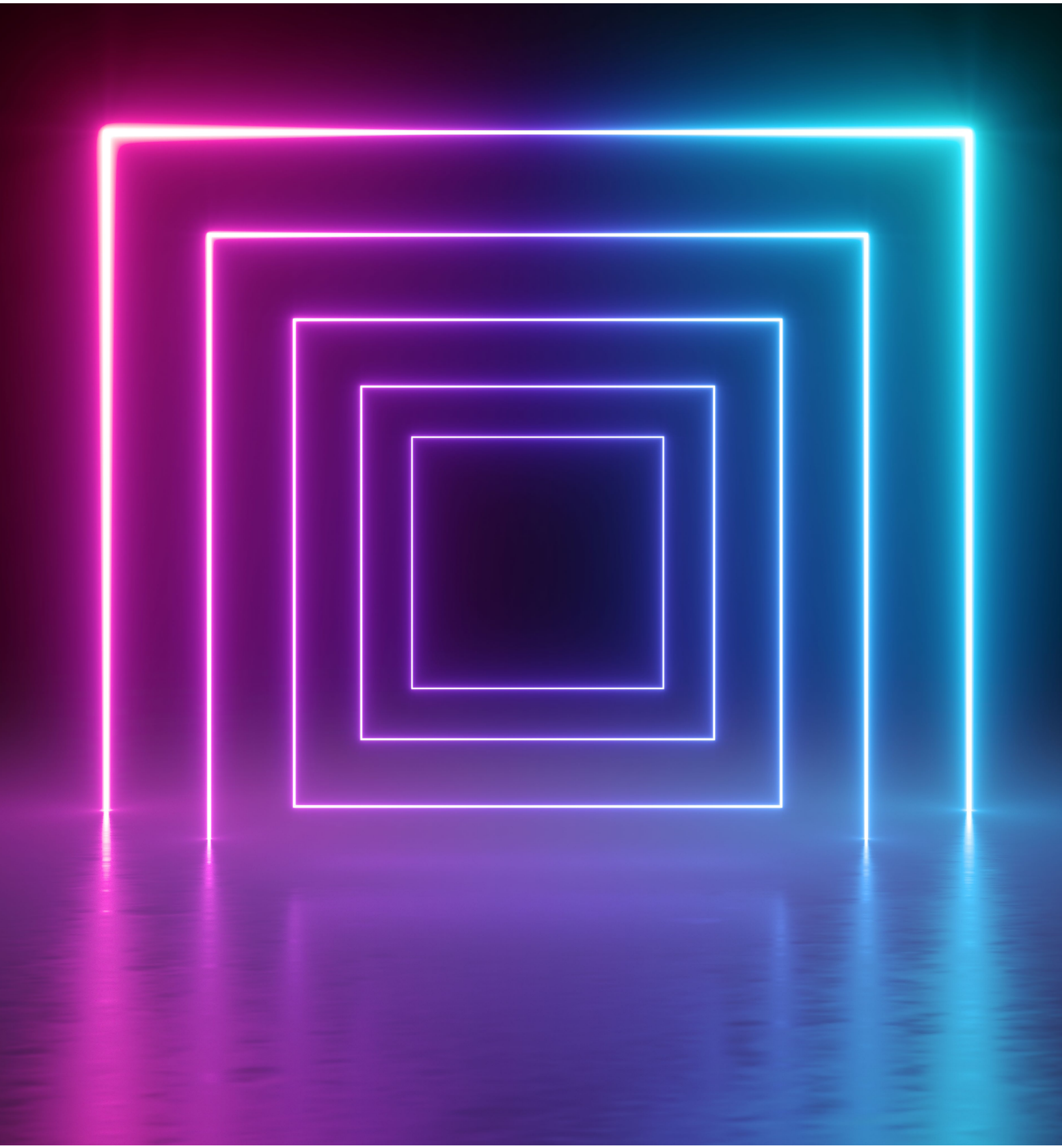
In this section we identified and analyzed 27 remedies that have the potential to overcome the obstacles reviewed in the Section 3. While these remedies are promising, there are still several challenges that prevent them from being implemented on a mass scale. In the next section, we'll synthesize the analysis of the obstacles and remedies into the grand challenges of longevity.



05.

GRAND CHALLENGES OF LONGEVITY

05



Introduction

IN THIS REPORT we have so far analyzed the key obstacles to a preferred future of longevity and examined the emerging and existing remedies that aim to overcome them. We now present five grand challenges of longevity, which together encapsulate the most critical obstacles and explain why the remedies are falling short.

Grand challenges are a combination of complex and overlapping social, technological, economic, environmental and policy issues. They provide both problems and opportunities for change. Were these challenges to be solved, researchers and innovators would gain powerful tools for advancing human longevity.

In addition to identifying the grand challenges of longevity, we also discuss the evident systemic failures—which we call gaps here—that perpetuate these grand challenges. Some gaps are shared by grand challenges, and are thus even more critical to solve.

WANT TO JUMP STRAIGHT TO THE BREAKTHROUGH SOLUTIONS? TURN TO PAGE 200 TO EXPLORE THE GAME-CHANGERS WE'VE IDENTIFIED THAT COULD SIGNIFICANTLY ACCELERATE THE FIELD OF LONGEVITY.

GRAND CHALLENGES OF LONGEVITY

Grand challenges are a combination of complex and overlapping social, technological, economic, environmental and policy issues. They provide both problems and opportunities for change. Were these challenges to be solved, researchers and innovators would gain powerful tools for advancing human longevity.

1

GRAND CHALLENGE #1:

ADVANCING SCIENTIFIC UNDERSTANDING OF THE AGING PROCESS

2

GRAND CHALLENGE #2:

IMPROVING TREATMENT TOOLS

3

GRAND CHALLENGE #3:

EXPEDITING DRUG DEVELOPMENT AND APPROVAL PROCESSES

4

GRAND CHALLENGE #4:

RAISING PUBLIC AWARENESS AND IMPROVING PUBLIC PERCEPTION

5

GRAND CHALLENGE #5:

ENSURING ACCESSIBILITY OF TREATMENTS

1

GRAND CHALLENGE #1

Advancing Scientific Understanding of the Aging Process

ALTHOUGH THE DISTILLATION of the formidably complex aging process into more manageable molecular and cellular changes has made creating longevity treatments much more viable, the aging process continues to mystify. Uncertainty remains, for example, about the cause and effect dynamics among the various changes that accompany aging. Such knowledge gaps slow progress in the field.

A critical component of advancing scientific understanding of the aging process would be the ability to quantify biological age. Currently, however, there is no one set of aging biomarkers that is widely accepted by the aging research community, and no single biomarker that can sufficiently reflect the complexity of the aging processes and mechanisms. Compounding this issue is the disagreement among experts about whether longevity studies and initiatives should focus on disease prevention, life extension, or age-reversal. Furthermore, the relative lack of formal training in aging and biogerontology among the medical community limits progress toward overcoming this grand challenge.

An improved understanding of how the different mechanisms and indicators of aging relate to each other would empower researchers and innovators to make more informed and effective decisions about how to intervene in the human aging process. While early treatments can certainly be discovered and developed in the absence of a complete understanding of the aging process (which indeed may prove so multifactorial and heterogenous that such a level of clarity is practically impossible), the more advanced scientific knowledge is of the aging process, the more sophisticated, efficient, and safe longevity treatments can become.

GAPS FOR ADVANCING SCIENTIFIC UNDERSTANDING OF THE AGING PROCESS

NO ACCURATE MODELS TO EXPERIMENT ON

There are currently no models that accurately reflect the complexity of the human body. As a result, experiments must be conducted on model animal organisms, simulations and organs-on-a-chip. The limitations of these models, including their relevance for translating science to humans, makes progress in the field exceedingly slow.

LACK OF FUNDING

The nature of basic science limits its potential for immediate profitability and utility, which can deter potential funders. Partly as a result of this, although many researchers study specific aging-related diseases, very few scientists study aging.

LACK OF CONSENSUS ON BIOMARKERS

Despite the existence of many potential aging biomarkers, none are sufficient for all purposes. There is a need to develop and rigorously evaluate new biomarkers for innate aging processes.

IMAGING TOOLS ARE LACKING IN CAPABILITIES

Imaging tools for intracellular processes, for example, can mainly function only on in-vitro samples. Tools for in-vivo imaging, however, are largely lacking in resolution and unable to delve into the inner workings of the cells. Thus, while limited assays like muscle biopsies or blood draws are useful to a degree, attempts to gain a better understanding of internal tissues and intracellular processes currently require sacrificing the experimental animal for dissection.

LIMITED HUMAN CAPACITY FOR UNDERSTANDING COMPLEX SYSTEMS

The human brain is limited by nature in its capacity to understand highly-complex systems. While AI engines are currently being developed to come up with more sophisticated models of biological processes, they are still in their infancy.

> "The lack of understanding the underlying fundamental biological mechanisms of aging is the biggest problem."
>
> **YURI DEIGIN,**
> CEO OF YOUTHEREUM GENETICS

2

GRAND CHALLENGE #2

Improving Treatment Tools

THERE ARE FEW available tools and methods that can be used to treat and counter the aging process. These processes are highly complex, and existing methods to treat them either lack the necessary precision or remain to be proven effective in large sample sizes.

Numerous tools are emerging—including genetic and epigenetic engineering, and stem cell therapy—but each treatment comes with limitations and risks. As a result, these tools currently struggle to achieve mainstream uptake.

A certain category of tools could help to circumvent the aging problem altogether by providing alternatives to the individual aging body. These concepts, like brain or head transplant and cryonics, are controversial and still in development, and key ethical questions must be addressed before such techniques become commonplace.

GAPS FOR IMPROVING TREATMENT TOOLS

TECHNOLOGICAL LIMITATIONS

For now, technologies like nano-robotics or brain transplant are simply not advanced enough for use.

RISKY TECHNOLOGY

Even state-of-the-art genetic engineering techniques still carry undeniable risk, which must be accounted for when considering whether to use them for treating aging. Similar risks exist for epigenetic engineering and stem cell therapies.

IDEOLOGICAL OBJECTIONS

The idea of life extension often invokes deep-seated fears and ideological objections, which makes it difficult for people to accept.

UNCLEAR ETHICS

The ethical aspects of any kind of engineering of the human body are controversial.

3

GRAND CHALLENGE #3

Expediting Drug Development and Approval Processes

THE CURRENT PROCESS for drug development and approval is exceedingly slow and expensive. This limits innovation to a select few players capable of bearing such investments. Even among those who can do so, the process is fraught with failures. At most, only 13.8% of all drug candidates that enter phase I of clinical trials end up being approved by the FDA. The entire process of clinical trials and FDA approval usually takes between six to 10 years. The fourth, post-market, phase can take up to 10 additional years. Other drug approval authorities worldwide impose similar timelines.

Trial duration, cost and low success rates are arguably a result of the scientific incentive system, which tends to discourage high-risk, high-reward studies. As a result, a greater proportion of the research that advances to a clinical trial has limited potential to produce statistically significant results. This is compounded by the tendency of researchers to refrain from sharing negative or inconclusive results, and the challenges of research study replication.[502]

Despite the tendency to blame the slow pace of drug development on the FDA, evidence shows that the agency tends to conduct the approval process with minimal delay once it receives the data from the clinical trials. Claims persist, however, that the process is excessively demanding. Some suggest that phase III could be eliminated altogether.

Nevertheless, consensus seems to be that the risks of drug development are unavoidable due to the high levels of uncertainty regarding how a drug candidate may impact the complexities of the human body.

Due to the high threshold for demonstrating safety and efficacy in human subjects, conducting a successful drug trial is exceptionally expensive. Drug development companies, motivated to recoup these costs, tend to pursue research and development that has a relatively immediate link to earning a return on investment. Such profit-seeking resource allocation is accompanied by the opportunity cost to society of firms not pursuing "basic science" to learn, for exam-

ple, more about the mechanisms of aging, which in turn holds back the entire field. Furthermore, firms are incentivized to develop drugs with the largest potential user base, but pursuing a one-size-fits-most solution appears to significantly lower the probability of success, especially given a heterogeneous population of interest.

To make matters worse, the FDA's requirement that drugs target a specific indication means that drugs targeting aging—which is not classified as a disease and is not considered an indication—will not receive regulatory approval. Firms are thus disincentivized from attacking aging "upstream."

Taken together, the heavy burden of earning regulatory approval and the framework of the regulations themselves pose significant hurdles to the development and dissemination of treatments, both for the consequences and especially for the causes of aging.

GAPS FOR EXPEDITING DRUG DEVELOPMENT AND APPROVAL PROCESSES

FLAWS IN THE INCENTIVE SYSTEM FOR SCIENTIFIC ACTIVITIES

Researchers' decisions about which topics to study are affected by the mandate to get publishable results, which discourages high-risk, high-reward studies and favors topics that are considered more conventional.

UNCLEAR DEFINITION OF AGING

Unlike many other conditions, aging is not defined as a treatable disease, and thus there is little incentive for pharma firms to focus on the field.

NO ACCURATE MODELS TO EXPERIMENT ON

There are currently no models that accurately reflect the complexity of the human body. As a result, experiments must be conducted on model animal organisms, simulations and organs-on-a-chip. The limitations of these models makes progress in the field exceedingly slow.

REGULATORY BUREAUCRACY

Any field in which a regulator requires firms to invest in navigating a bureaucratic maze is largely closed to new and young challengers that lack the funding and experience to compete in the arena.

LACK OF FUNDING

A substantial amount of time and money needs to be invested into the drug development and approval process. Financing the process often requires having multiple funding streams, and assuming the risks of uncertain return on investment.

4

GRAND CHALLENGE #4

Raising Public Awareness and Improving Public Perception

THE GENERAL PUBLIC is largely unaware of longevity science, and is oblivious to the potential it holds for improved quality of life. Articles that expose laypeople to news about longevity science and developments are often written in a sensationalistic manner that either emphasizes the negative potential impact of life extension treatments or dismisses the idea altogether. Moreover, the implications of extending human life and lifespan are colored by numerous viewpoints and can be interpreted through virtually every possible cultural, religious, philosophical, and ethical lens.

The result of this situation is that there is a lack of public and political will toward funding longevity studies. Limited public pressure also means that some highly-needed legal arrangements about longevity studies are not being fulfilled: aging, for example, has yet to be classified as a disease. Thus, even pharmaceutical companies hesitate to develop drugs in this sector, as it is not clear whether there will be a regulatory path for them. It is likely that without greater public acceptance and pressure, many governing bodies will overlook or even disregard developments in the field.

GAPS FOR RAISING PUBLIC AWARENESS AND IMPROVING PUBLIC PERCEPTION

MISINFORMATION

Longevity advocates are often confused with organizations that focus on selling supplements with controversial impact on aging, which can tarnish their reputation.

IDEOLOGICAL OBJECTIONS

The idea of life extension often invokes deep-seated fears and ideological objections, which makes it difficult for people to accept. Longevity advocates often do not sufficiently address these fears and objections.

NEGATIVE PERCEPTION OF LIFE EXTENSION ADVOCATES

Advocates of life extension often use radical messaging and as a result tend to be portrayed by the media in a belittling light. Even when they're being covered fairly, the main focus is often on their eccentricities.

LACK OF INFORMATION

The public is not well educated about the biology of aging or the possibility of manipulating it. There are few if any entities that can credibly and widely communicate the advancements and developments in the field.

LACK OF FUNDING

Longevity advocacy organizations often struggle to raise funding for public relations to influence the public mood and mindset, and to implement effective management practices.

5

GRAND CHALLENGE #5

Ensuring Accessibility of Treatments

LONGEVITY TREATMENTS SHOULD eventually be accessible to all. Medical treatments, however, are typically expensive when they're first released to the market, often due to the high development costs and patent protections. High prices for longevity treatments may mean that many people will not be able to afford them, which could breed greater social and economic disparities in virtually every part of the world.

This issue may resolve itself in time—whether by the eventual expiration of patents, government subsidies, or having pharmaceutical firms set affordable drug prices. It's clear, however, that the issue of accessibility of treatments needs to be addressed in every serious discussion about longevity.

Even if this concern is unfounded—as many say it is—the fact that it is so rampant emphasizes the importance of this challenge. If it goes unaddressed, this concern will likely limit the public support that may be necessary to accelerate research and development as well as productive legislative changes

Another difficulty in ensuring the accessibility of treatments is that most medical doctors receive almost no training in aging and biogerontology, and so do not realize that tackling aging is the best way to tackle many aging-related diseases. Medical doctors are often ignorant of the new breakthroughs in aging research, and thus look down upon or discard notions that aging can be addressed. Even when they're aware of the longevity potential of some drugs, they may find it difficult to prescribe them to patients who are not yet diagnosed with any sort of sickness, but are only experiencing "natural" aging.

GAPS FOR ENSURING ACCESSIBILITY OF TREATMENTS

DEALING WITH EXPENSIVE TREATMENTS

Governments, pharmaceutical companies and insurance companies need to find the right balance for treatment prices, in a way that promotes accessibility without discouraging innovation.

INTEGRATION INTO HEALTHCARE SYSTEMS

Potential longevity treatments will need to be integrated into the current healthcare and patient-care systems. It is unclear whether such treatments would be considered optional or fully integrated as standards for treating existing diseases.

METHODS OF DISTRIBUTION

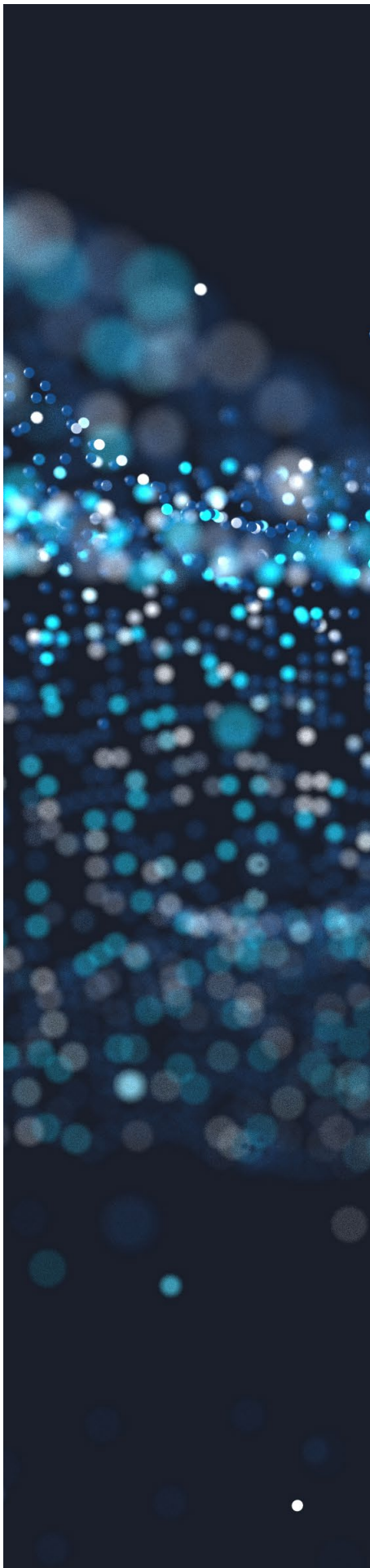
Treatments will need to be safely delivered to developing countries. Such deliveries may face harsh conditions, such as inclement weather and inadequate infrastructure.

LAWS

There are no established laws that will legally ensure and protect accessibility rights.

Conclusion

In this section we've identified and analyzed the five grand challenges of longevity, and the main reasons why we struggle to solve them. In the next section, we'll detail several future breakthrough solutions that have the potential to overcome these grand challenges.



06.

BREAKTHROUGHS FOR LONGEVITY

06

Introduction

XPRIZE WAS FOUNDED to leverage and incentivize the use of exponential technologies to positively transform the world. In the previous section, we identified and analyzed the grand challenges we must overcome to achieve a preferred future of longevity.

Breakthroughs are the solutions to these challenges. They represent our path to a better future.

In this section, we propose 12 breakthroughs that could overcome the grand challenges of longevity. We explain the significance and importance of each breakthrough, and provide examples of technologies that could be used to achieve them.

Method for Identifying Breakthroughs

Breakthroughs are grand solutions to grand challenges. They are transformational achievements that overcome the issues most people believe are unsolvable.

PRECISELY BECAUSE OF their grand nature and incredible results, breakthroughs often do not come from the establishment but instead from bold entrepreneurs, innovators and inventors. This is why XPRIZE is dedicated to harnessing the passion and wisdom of the crowd.

Through a combination of horizon scanning, interviews, and crowdsourced research, we have identified several breakthroughs to overcome the grand challenges of longevity. We also conducted a survey of nearly 100 multidisciplinary experts, in which we asked each respondent to forecast, for each Breakthrough:

» The year a proof-of-concept (POC) will be demonstrated

» The year that a scalable solution will be available

» The impact on a 1-to-10 scale

» The audacity on a 1-to-10 scale

The survey results are included in the analyses below.

These 12 Breakthroughs are meant to spark innovation and encourage the pursuit of these ideas. This list, however, is far from "final"–we are confident there are many other ideas out there, and we encourage our readers and supporters to suggest additional breakthroughs and expand on those included here.

We present the breakthroughs in order from earliest-expected proof-of-concept to latest, based on the median survey data.

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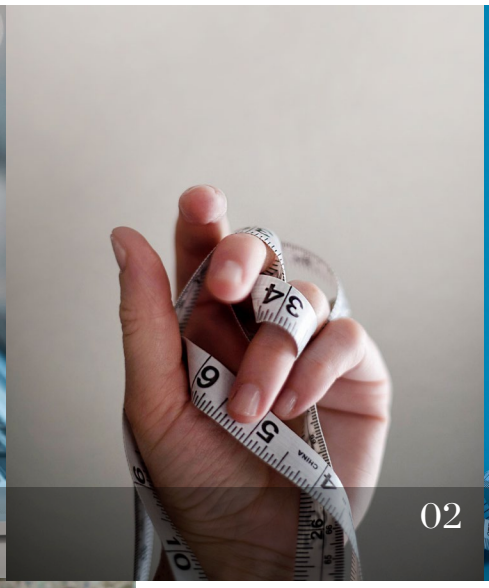

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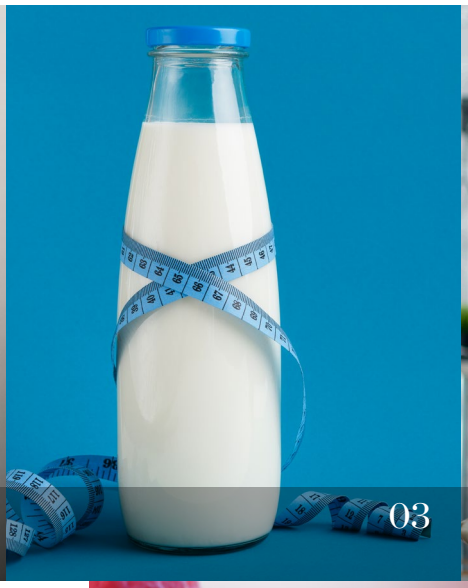

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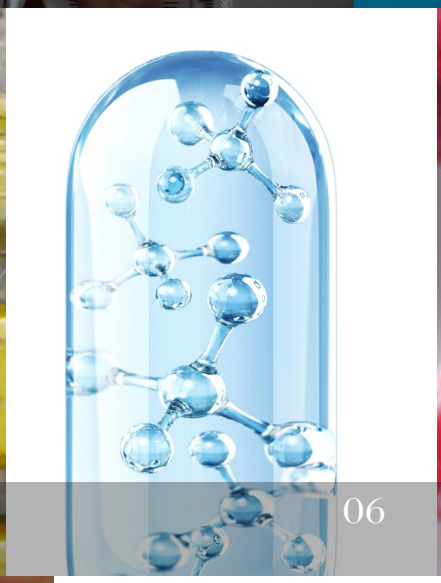

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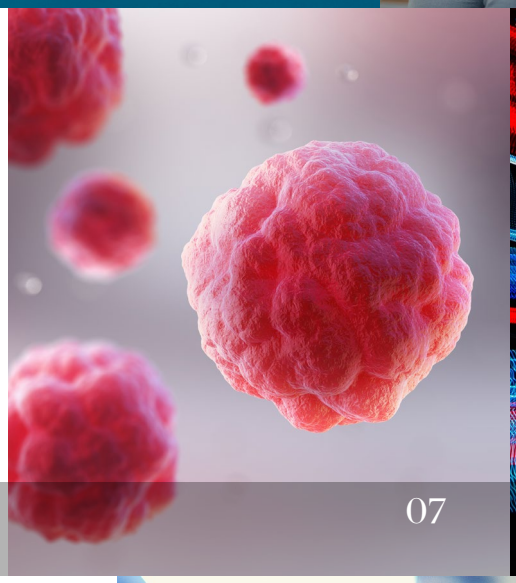

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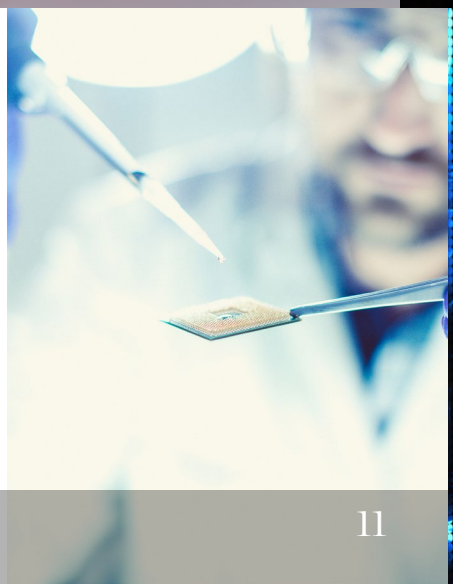

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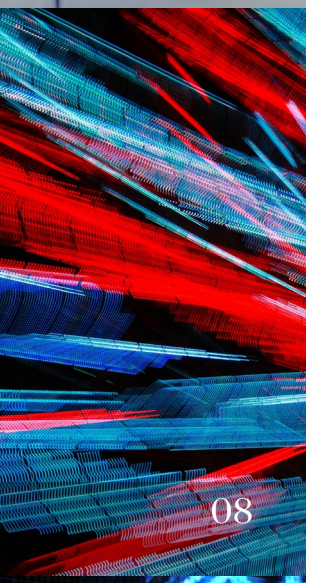
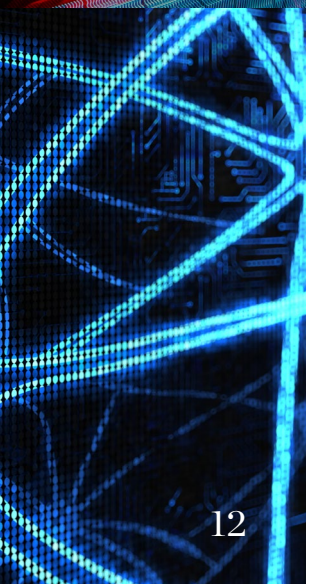




Breakthroughs

BREAKTHROUGH 01

Aging, Shared

A shared database to collect real-time aging data

SURVEY RESULTS

» **EXPECTED YEAR FOR PROOF OF CONCEPT**: 2022

» **EXPECTED YEAR FOR MASS-SCALING**: 2030

» **IMPACT (1-10)**: 5.5

» **AUDACITY (1-10)**: 4.5

OUTCOME

A ledger in which real-time data will be collected from individuals, to track their vital signs and lifestyle choices and activities.

WHY THE NEED?

There are currently very few options to collect real-time health-related data about individuals. When such data are collected via multiple wearables, it is often difficult to consolidate them onto a single database, where they can be matched with the person from which they originated. A shared ledger could collect and store this kind of information in a secure way that ensures the participants' anonymity and privacy. The data could then be used to:

» Help researchers develop potential new treatments to aging

» Personalize medications for older adults in a time-resolution of minutes

» Raise awareness about the aging process that every individual experiences throughout their lives

RELEVANT GRAND CHALLENGES

» Advancing Scientific Understanding of the Aging Process

» Improving Treatment Tools

» Expediting Drug Development and Approval Processes

» Raising Public Awareness and Improving Public Perception

» Ensuring Accessibility of Treatments

STIPULATIONS FOR A SUCCESSFUL BREAKTHROUGH SOLUTION

» The ledger must be secure from hacking

» The ledger should not be maintained by any pharmaceutical firm, governmental department, or central authority

» The ledger must be anonymized to all but the end users (those who've allowed their data to be collected in the database)

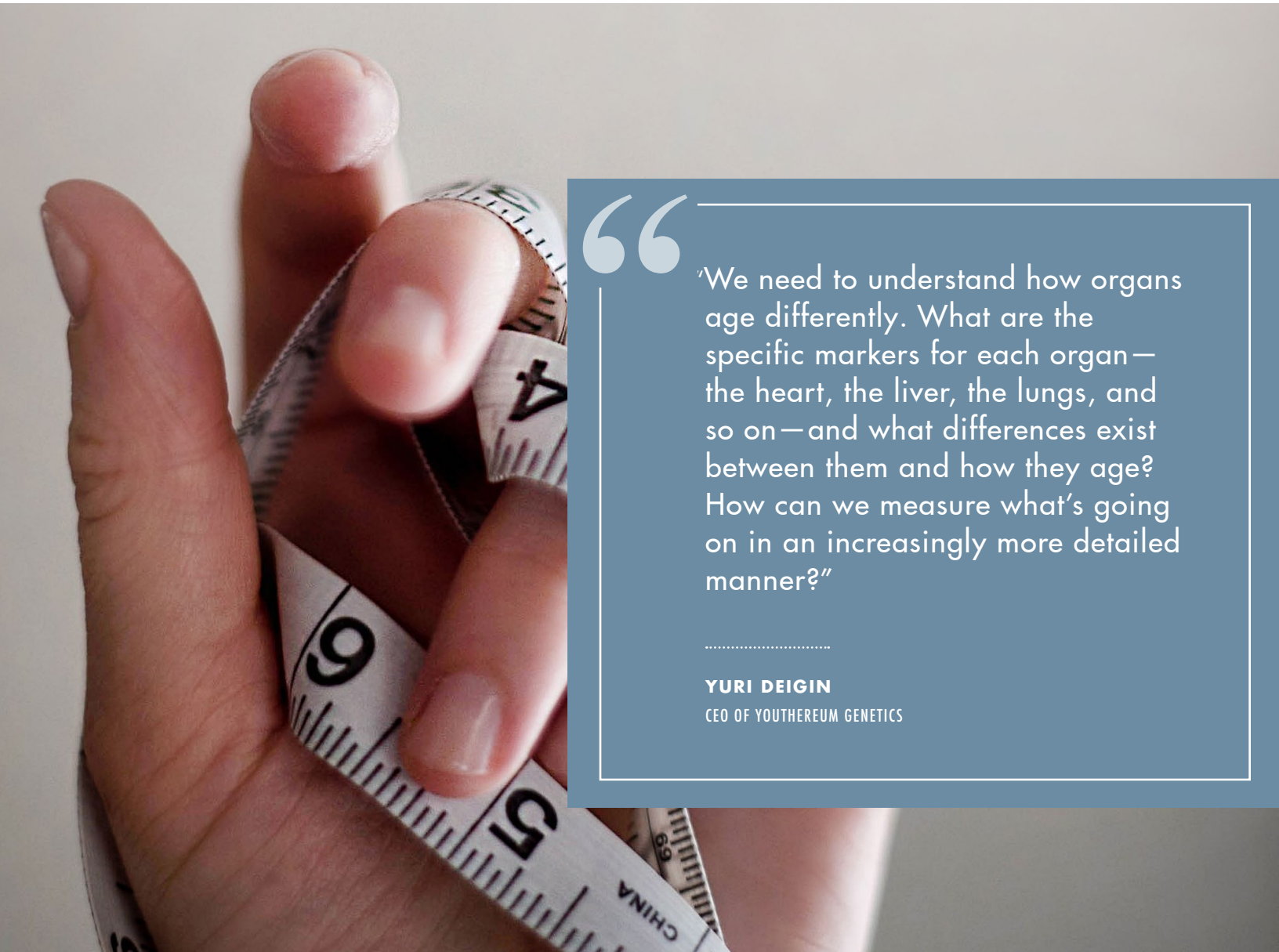
PROMISING TECHNOLOGIES FOR SOLUTIONS

Blockchain technologies seem to currently have the best potential to fulfill the requirements of this breakthrough. Other technologies, however—existing or hypothetical—that enable the creation of a shared ledger should not be discounted out of hand.

BREAKTHROUGH 02

Aging, Quantified

A set of widely agreed-upon biomarkers for measuring biological age



> "We need to understand how organs age differently. What are the specific markers for each organ—the heart, the liver, the lungs, and so on—and what differences exist between them and how they age? How can we measure what's going on in an increasingly more detailed manner?"
>
> **YURI DEIGIN**
> CEO OF YOUTHEREUM GENETICS

SURVEY RESULTS

» **EXPECTED YEAR FOR PROOF OF CONCEPT**: 2025

» **EXPECTED YEAR FOR MASS-SCALING**: 2030

» **IMPACT (1-10)**: 6

» **AUDACITY (1-10)**: 5

OUTCOME

A set of aging biomarkers that will be accepted by the community of longevity and aging researchers and utilized as a benchmark in any research and development in the field.

WHY THE NEED?

There is currently much confusion and disagreement about the best way to quantify biological age. It seems clear that no single biomarker can shed enough light on the aging process, but no set of aging biomarkers has yet to be accepted by the longevity and aging research community. Without a well established set of aging biomarkers, it is nearly impossible to precisely quantify one's biological age, and to understand how well a certain treatment works. A set of aging biomarkers would also help in raising public awareness of the issue of aging, as individuals will be able to easily ascertain their own biological ages.

RELEVANT GRAND CHALLENGES

» Advancing Scientific Understanding of the Aging Process

» Expediting Drug Development and Approval Processes

» Raising Public Awareness and Improving Public Perception

» Ensuring Accessibility of Treatments

STIPULATIONS FOR A SUCCESSFUL BREAKTHROUGH SOLUTION

The set of biomarkers must fit the criteria established by the AFAR, according to which the biomarker or set of biomarkers:

» Must predict a person's physiological, cognitive, and physical function in an age-related way

» Must be testable and not harmful to test subjects, as well as technically simple to perform

» Should work on animals as well as humans

Finally, the aging biomarkers should be able to reflect a reversal of the aging process.

PROMISING TECHNOLOGIES FOR SOLUTIONS

A comprehensive review of candidate biomarkers of aging has concluded that epigenetic clocks based on DNA methylation levels constitute the most promising biomarkers of aging.[503] The predictive utility of some epigenetic clocks has been validated in large cohorts and large sample sizes.[504] These epigenetic clocks are already being used in human clinical trials of anti-aging interventions.

While standard clinical biomarkers and DNA methylation-based biomarkers are arguably necessary biomarkers of aging for future clinical trials, it is "unlikely that they are sufficient for quantifying biological age, and thus the need to develop and validate additional biomarkers of aging.

BREAKTHROUGH 03

Caloric Restriction for All

Replicating the beneficial effects of caloric restriction, without the negative effects

SURVEY RESULTS

» **EXPECTED YEAR FOR PROOF OF CONCEPT**: 2025

» **EXPECTED YEAR FOR MASS-SCALING**: 2030

» **IMPACT (1-10)**: 5.5

» **AUDACITY (1-10)**: 5

OUTCOME

A treatment, diet regime or biomedical device that can replicate the beneficial effects of caloric restriction, without the negative effects.

WHY THE NEED?

Caloric restriction, which includes intermittent fasting and time-restricted eating, is gaining popularity as a way to tailor one's diet to impact lifespan and healthspan. These dietary regimens, however, are difficult for the body to maintain for extended periods of time, and they require lifestyle choices that many people may find too inconvenient or unable to follow due to other health reasons. A solution is needed that provides the beneficial effects of caloric restriction and intermittent fasting without [1] requiring the user to fast or diet, or [2] having the negative side effects associated with caloric restriction, such as loss of bone density and lean muscle mass.

Any solution that accomplishes one of these requirements will enable many to enjoy the benefits of this remedy.

RELEVANT GRAND CHALLENGES

» Improving Treatment Tools

» Raising Public Awareness and Improving Public Perception

» Ensuring Accessibility of Treatments

STIPULATIONS FOR A SUCCESSFUL BREAKTHROUGH SOLUTION

» The solution will be safe for use

» The solution will provide the benefits of caloric restriction without the need for extraordinary willpower

» The solution will mitigate as many negative effects of caloric restriction as possible

PROMISING TECHNOLOGIES FOR SOLUTIONS

Promising technologies include food engineering, to create food that can trick the brain into feeling satiated. More radical techniques may include a non-intrusive way to minimize the volume of a person's stomach, or some other way to provide a feeling of being satiated. Even lifestyle and "quantified self" apps and sensors may provide a solution, though their advice must not cause harm to the users.

BREAKTHROUGH 04

Preparing for Aging

Early diagnosis of aging-related diseases and conditions

SURVEY RESULTS

» **EXPECTED YEAR FOR PROOF OF CONCEPT**: 2025

» **EXPECTED YEAR FOR MASS-SCALING**: 2030

» **IMPACT**: 6

» **AUDACITY**: 5

OUTCOME

A method or tool for early diagnosis of at least three aging-related diseases and conditions. The breakthrough will provide an earlier and more accurate diagnosis than any of the other commonly used methods employed today.

WHY THE NEED?

An early diagnosis of aging-related diseases and conditions could help to gain a better understanding of their cause and progression, and deal with their consequences more efficiently. Today's treatments are often not advanced enough to deal with aging-related diseases or conditions, even those discovered earlier than usual. This breakthrough, therefore, will be all the more effective alongside the further development of treatments.

An early diagnosis could also help develop tools to better understand the underlying indicators and mechanisms of aging. Finally, it will increase public awareness of aging, as people will more readily realize their place on the aging spectrum, sometimes even as early as the third decade of their lives.

RELEVANT GRAND CHALLENGES

» Advancing Scientific Understanding of the Aging Process

» Improving Treatment Tools

» Raising Public Awareness and Improving Public Perception

STIPULATIONS FOR A SUCCESSFUL BREAKTHROUGH SOLUTION

» Must be testable and not harmful to test subjects, as well as technically simple to perform

» Should work on animals as well as humans

PROMISING TECHNOLOGIES FOR SOLUTIONS

There are many diagnostic technologies that could be used to accomplish this breakthrough. These include DNA sequencing, real-time epigenomics mapping, tracking aging biomarkers, advanced imaging technologies, and others. This breakthrough will likely be achieved via a combination of several of these techniques.

BREAKTHROUGH 05

The Age-Reversed Animal

Demonstrating age-reversal in an animal model

SURVEY RESULTS

» **EXPECTED YEAR FOR PROOF OF CONCEPT**: 2025

» **EXPECTED YEAR FOR MASS-SCALING**: 2035

» **IMPACT (1-10)**: 6.5

» **AUDACITY (1-10)**: 6.5

OUTCOME

An animal model whose normal biological age is reversed by an intervention that can be repeated at least once.

WHY THE NEED?

There is a need to demonstrate new capabilities and opportunities that the field of longevity and age-reversal opens for humankind. An animal whose aging can be effectively reversed, such that its rejuvenation makes it highly similar to a younger organism, will provide a powerful demonstration of the promise of age-reversal for human beings, and will demonstrate a better and more holistic understanding of the aging process.

RELEVANT GRAND CHALLENGES

» Advancing Scientific Understanding of the Aging Process

» Raising Public Awareness and Improving Public Perception

STIPULATIONS FOR A SUCCESSFUL BREAKTHROUGH SOLUTION

» The age-reversed animal should be as advanced as possible–up to the primate level

» The longer the animal lives (i.e., the more youth-age-youth cycles it undergoes), the better

» The animals must be experimented upon in an ethical and humane fashion as much as possible

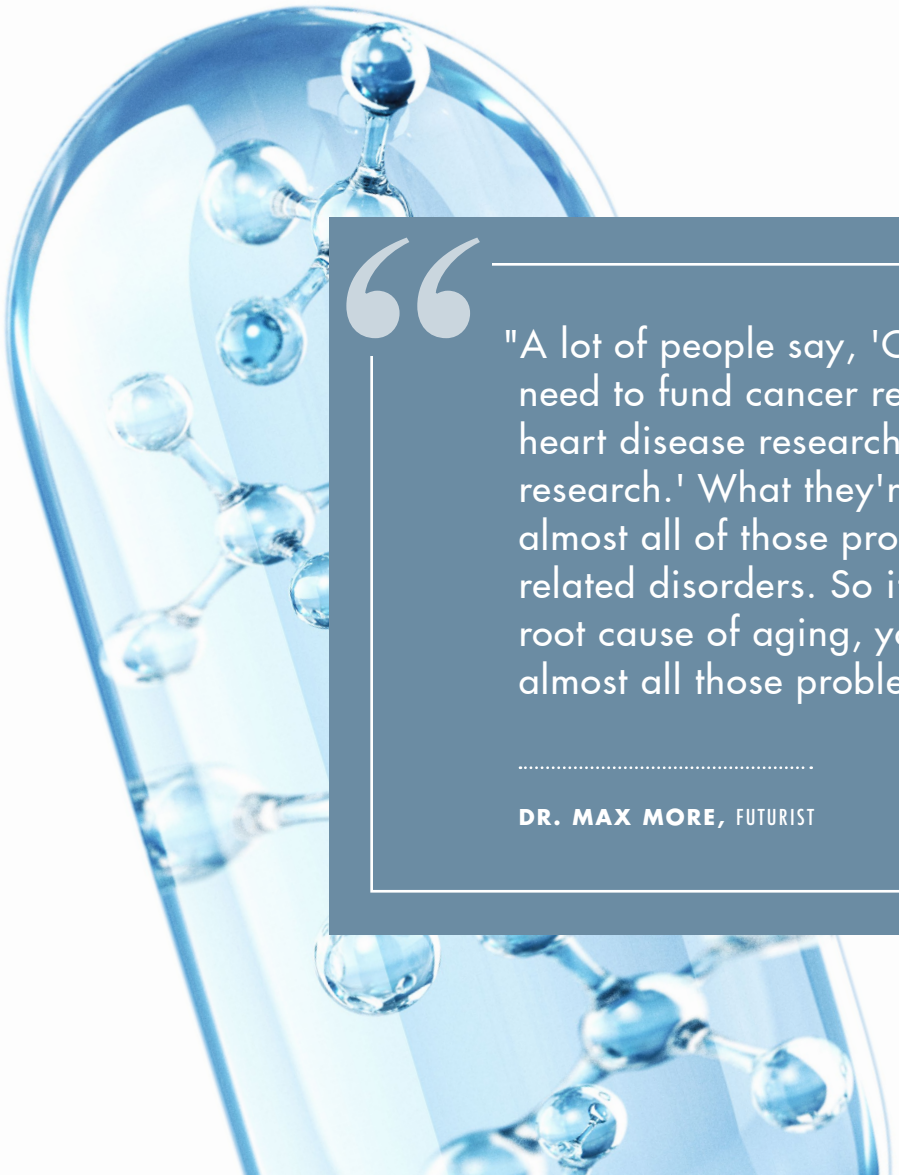
PROMISING TECHNOLOGIES FOR SOLUTIONS

There are many technologies and drug candidates that have the potential to achieve at least parts of this breakthrough. It seems likely that genetic engineering will need to be used in order to produce the first "immortal mouse". It is important, however, that any such engineering be implemented in adult animals, rather than built into them from conception, because the latter is significantly easier and less relevant to humans.

BREAKTHROUGH 06

Aging, Delayed

Postponing the emergence of at least three aging-related diseases or conditions with the same treatment



> "A lot of people say, 'Oh, yeah, we need to fund cancer research, and heart disease research, and Alzheimer's research.' What they're not getting is almost all of those problems are aging-related disorders. So if we tackle the root cause of aging, you can abolish almost all those problems."
>
> **DR. MAX MORE,** FUTURIST

SURVEY RESULTS

» **EXPECTED YEAR FOR PROOF OF CONCEPT**: 2030

» **EXPECTED YEAR FOR MASS-SCALING**: 2035

» **IMPACT (1-10)**: 7

» **AUDACITY (1-10)**: 6

OUTCOME

Postponing the emergence of at least three aging-related diseases or conditions with the same treatment. This will demonstrate that the emergence of aging-related diseases and conditions can be postponed and delayed, not one disease at a time, but instead by targeting more upstream factors related to aging.

WHY THE NEED?

Postponing the emergence of even a single aging-related disease or condition would be a great boon to humanity. While this result would obviously be highly beneficial to humankind, demonstrating that multiple aging-related diseases can be postponed with one treatment would be even more impactful. The general public will see with great clarity that aging-related diseases are interconnected and treatable. The ensuing zeitgeist will be one of hope and optimism, expressed by the public in a way that will require politicians and decision-makers to direct funding into longevity and age-reversal research.

RELEVANT GRAND CHALLENGES

» Improving Treatment Tools

» Raising Public Awareness and Improving Public Perception

STIPULATIONS FOR A SUCCESSFUL BREAKTHROUGH SOLUTION

» The emergence of at least three aging-related diseases or conditions must be delayed with the same treatment

» The treatment must be demonstrated on a "higher mammal" model: dogs, primates, or even humans

» The results of the treatment must be objectively verified and statistically approved

» The treatment in question cannot consist of lifestyle choices (physical exercise, dietary restriction, etc.), as these are already available, but have not been widely adopted

PROMISING TECHNOLOGIES FOR SOLUTIONS

Certain drugs and drug candidates—like rapamycin and metformin—seem likely to have this effect in animals and in human beings. Other molecules that are only now being discovered and assessed—like GDF11—may have a similar effect as well.

BREAKTHROUGH 07

Homeostasis Restored

Constant analysis of the body's capacity to uptake nutrients and the bioavailability of critical biomolecules

> "It is only a matter of time before we are able to monitor important aspects of our metabolic homeostasis, and then act on those implications, without requiring medical advice."
>
> **DR. BOB DAY,** FUTURIST

SURVEY RESULTS

» **EXPECTED YEAR FOR PROOF OF CONCEPT**: 2030

» **EXPECTED YEAR FOR MASS-SCALING**: 2035

» **IMPACT (1-10)**: 6

» **AUDACITY (1-10)**: 5.5

OUTCOME

A solution that will analyze people's capacity to uptake nutrients, as well as the bioavailability of critical biomolecules in their body, and provide actionable advice on how to restore youthful levels.

WHY THE NEED?

During the aging process, the body loses some of its capacity to take up various nutrients, including certain minerals and vitamins. The levels of other molecules important for optimal metabolism, like NAD, often decline as well. Low levels of these substances are associated with aging, and their supplementation is suspected of aiding in postponing the emergence of aging-related diseases and conditions. It is likely that the loss of homeostasis of these molecules accelerates biological aging. This deficiency can be mitigated, however, through a solution that can analyze the body at any given time and recommend supplementation and personalized medicines to restore youthful homeostasis.

RELEVANT GRAND CHALLENGES

» Advancing Scientific Understanding of the Aging Process

» Improving Treatment Tools

» Expediting Drug Development and Approval Processes

» Raising Public Awareness and Improving Public Perception

» Ensuring Accessibility of Treatments

STIPULATIONS FOR A SUCCESSFUL BREAKTHROUGH SOLUTION

» The solution must be easy to use and widely accessible

» The solution must be as non-intrusive as possible

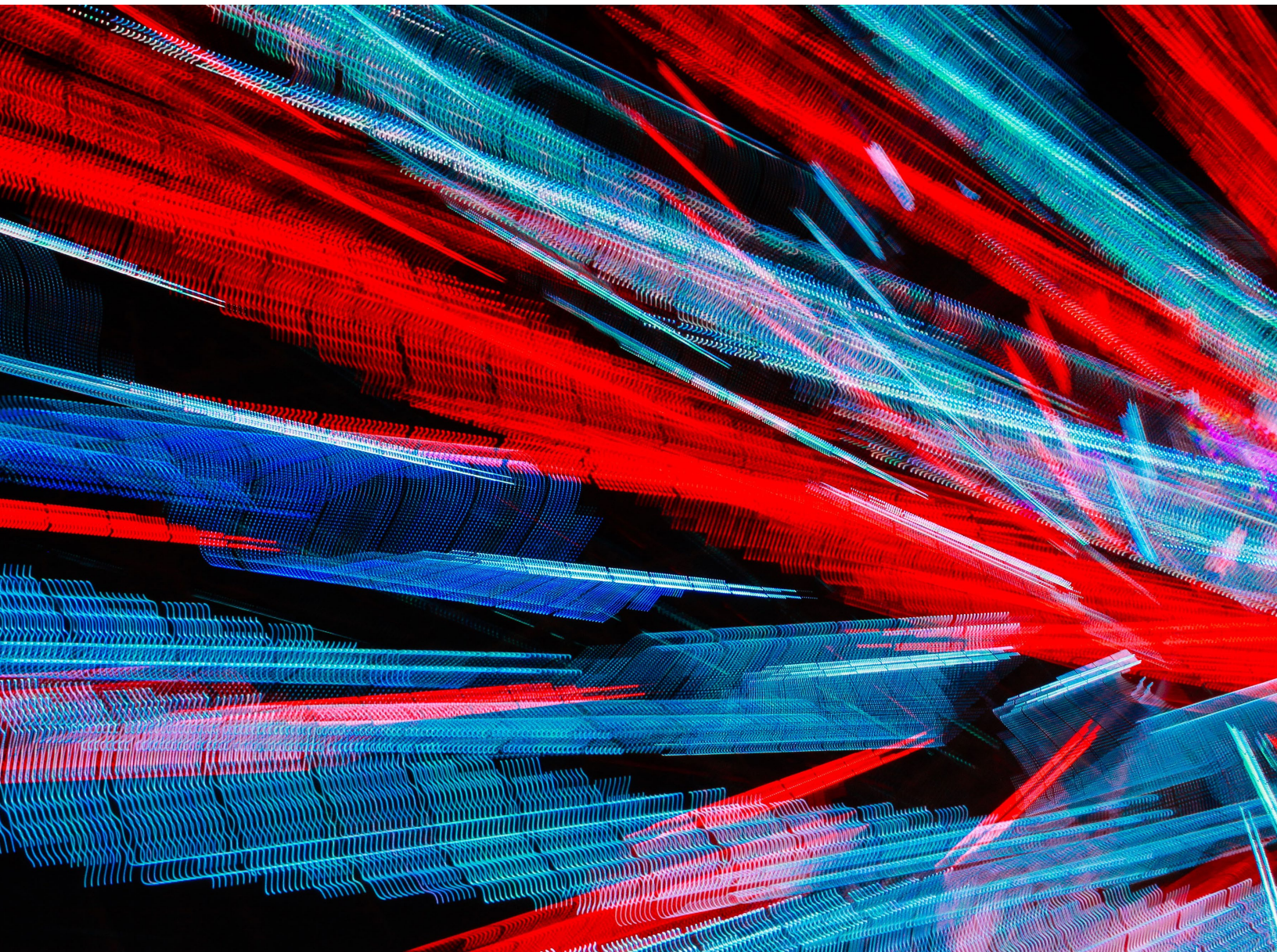
PROMISING TECHNOLOGIES FOR SOLUTIONS

Promising technologies include the use of wearables, ingestibles and embeddables to quantify food consumption and equate it with the actual nutrient uptake and weight gain. The data collected via these devices will likely be analyzed by powerful AI engines—partly to make sense of the correlations between the different parameters and factors, and partly to analyze visual, auditory and other forms of data that are being gathered from the body and the surrounding environment.

BREAKTHROUGH 08

Aging, Understood

A Robust Theory of Aging



SURVEY RESULTS

» **EXPECTED YEAR FOR PROOF OF CONCEPT**: 2030

» **EXPECTED YEAR FOR MASS-SCALING**: 2040

» **IMPACT (1-10)**: 7

» **AUDACITY (1-10)**: 6.5

OUTCOME

A theory of aging that ties together all the different mechanisms of aging and explains the relationship between them. The theory will predict how any change of the involved factors will affect the aging process.

WHY THE NEED?

There's currently no robust theory of aging that explains how the mechanisms of aging influence each other, the body, and the aging process. Without such a theory, attempts to significantly slow down or even reverse aging retain high risks of unknown negative side effects and dead-end research. A robust theory will help scientists better understand the aging process and will guide drug developers and biomedical engineers in their attempts to slow down or reverse aging.

RELEVANT GRAND CHALLENGES

» Advancing Scientific Understanding of the Aging Process

» Expediting Drug Development and Approval Processes

STIPULATIONS FOR A SUCCESSFUL BREAKTHROUGH SOLUTION

» The theory must tie together all known indicators of aging, or explain why some are left out

» The theory must be explainable and quantifiable, so that it can be used to predict future occurrences and the result of any intervention

» The theory does not have to describe *human* aging, but the more advanced the animal it describes, the better

PROMISING TECHNOLOGIES FOR SOLUTIONS

It is likely that the creation of such a theory will require the use of sophisticated artificial intelligence and machine learning engines, coupled with insights gained from the world's longevity and aging researchers.

BREAKTHROUGH 09

Exercise Made Easy

Replicating the beneficial effects of exercise, without the need to exert the body

SURVEY RESULTS

» **EXPECTED YEAR FOR PROOF OF CONCEPT**: 2030

» **EXPECTED YEAR FOR MASS-SCALING**: 2040

» **IMPACT (1-10)**: 6

» **AUDACITY (1-10)**: 6

OUTCOME

A treatment or biomedical device that can replicate the beneficial effects of exercise, without the user having to exert their body.

WHY THE NEED?

Physical exercise is well accepted as positively impacting both lifespan and healthspan. However, it requires willpower, time, experience or guidance, and general good health from the get-go. It is therefore difficult to massively scale its benefits.

RELEVANT GRAND CHALLENGES

» Improving Treatment Tools

» Raising Public Awareness and Improving Public Perception

» Ensuring Accessibility of Treatments

STIPULATIONS FOR A SUCCESSFUL BREAKTHROUGH SOLUTION

» The solution will be safe for use

» The solution will provide the benefits of physical exercise without the need for free time, willpower, expert guidance or good health

PROMISING TECHNOLOGIES FOR SOLUTIONS

There are many ideas for the technologies that could form the basis for this breakthrough. Electric or physiological muscle stimulation, for example, might have a similar effect as that of physical exercise. Exoskeletons may be utilized for such purposes. Alternatively, affecting the metabolic pathways involved in the beneficial effects of physical exercise may also provide a viable solution.

BREAKTHROUGH 10

Aging, Arrested

Stopping the body's aging process for at least one year

SURVEY RESULTS

» **EXPECTED YEAR FOR PROOF OF CONCEPT**: 2035

» **EXPECTED YEAR FOR MASS-SCALING**: 2048

» **IMPACT (1-10)**: 6.5

» **AUDACITY (1-10)**: 7

OUTCOME

A treatment for completely stopping the body's aging process for at least one year. The treatment will likely be demonstrated on mammals first, and will later be translated to human beings.

WHY THE NEED?

By halting the aging process, even temporarily and in animal models only, a first proof of concept will be procured for the chance to stop aging in human beings. Additionally, the lessons obtained from stopping aging in animals will help provide a better understanding of the aging process in humans. Finally, the animals in which aging has been stopped could be used as new and more efficient models on which to test longevity drug candidates.

RELEVANT GRAND CHALLENGES

» Advancing Scientific Understanding of the Aging Process

» Expediting Drug Development and Approval Processes

» Raising Public Awareness and Improving Public Perception

STIPULATIONS FOR A SUCCESSFUL BREAKTHROUGH SOLUTION

» The animal should be as advanced as possible—up to the primate level

» The longer the aging process is halted for, the better

» The animals must be experimented upon in an ethical and humane fashion as much as possible

PROMISING TECHNOLOGIES FOR SOLUTIONS

There are many technologies and drug candidates that have the potential to achieve at least parts of this breakthrough. It also seems likely that genetic engineering will need to be used in order to produce a more-or-less "ever-living" animal.

BREAKTHROUGH 11

In Silico Aging

Creating a detailed and accurate model of the human body, for high-capacity in-vitro experimentation

SURVEY RESULTS

» **EXPECTED YEAR FOR PROOF OF CONCEPT**: 2040

» **EXPECTED YEAR FOR MASS-SCALING**: 2045

» **IMPACT (1-10)**: 6

» **AUDACITY (1-10)**: 7

OUTCOME

A model of the human body that is detailed and accurate enough to replace some experimentation on mammalian models and even human beings with in-vitro experimentation and clinical trial simulation.

WHY THE NEED?

Drug development and approval processes are expensive and take a long time, and many drug candidates fail to complete the process successfully. Part of the problem is that there are no good models to reliably test new drug candidates on in the lab, as animal models do not accurately reflect the complexity of the human body. Current labs-on-a-chip are not sophisticated and/or cheap enough to be widely used. Creating a detailed and accurate model of the human body could dramatically accelerate the development and approval of new drugs, including ones that induce longevity and age-reversal.

RELEVANT GRAND CHALLENGES

» Advancing Scientific Understanding of the Aging Process

» Expediting Drug Development and Approval Processes

STIPULATIONS FOR A SUCCESSFUL BREAKTHROUGH SOLUTION

» The model must be more accurate and detailed than existing ones

» The model must be cost-competitive enough to be used by any biomedical lab or biotech start up

» The model should accelerate, and possibly even disrupt (by allowing everyone to experiment), the current drug R&D and approval process.

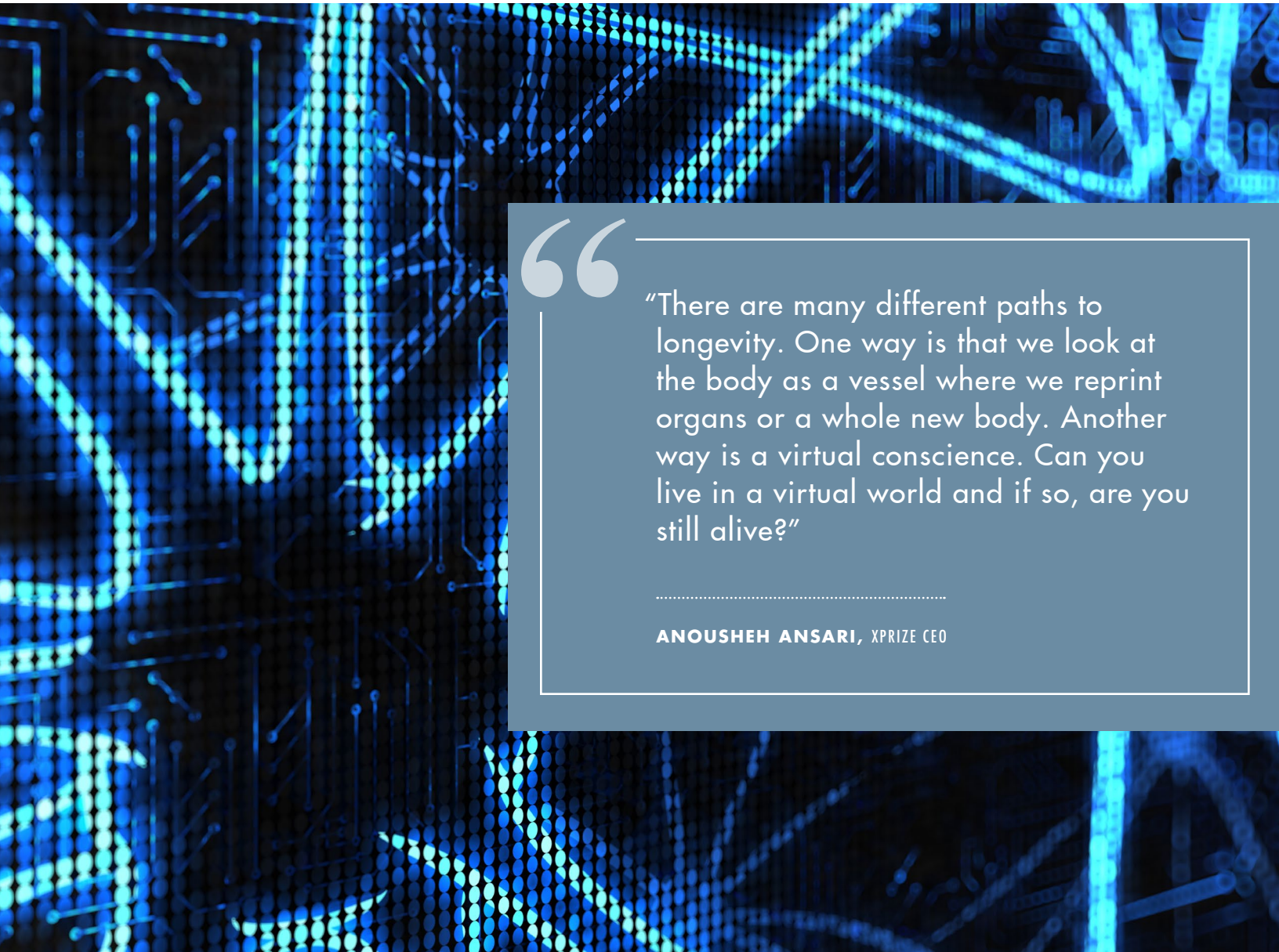
PROMISING TECHNOLOGIES FOR SOLUTIONS

Lab-on-a-chip technology is likely to play a part in the construction of any physical model, in which actual drugs and molecules will be tested. The actual internal structure of the lab-on-a-chip, however, will need to simulate multiple tissues and organs, as well as "blood" circulation throughout the tissues. Promising technologies for the fabrication of a lab-on-a-chip of this level of sophistication will probably entail nano-technological fabrication processes, 3D printing, artificial intelligence, tissue engineering and others.

BREAKTHROUGH 12

Aging, Circumvented

A way to safely detach the brain from the aging body



> "There are many different paths to longevity. One way is that we look at the body as a vessel where we reprint organs or a whole new body. Another way is a virtual conscience. Can you live in a virtual world and if so, are you still alive?"
>
> **ANOUSHEH ANSARI,** XPRIZE CEO

SURVEY RESULTS

» **EXPECTED YEAR FOR PROOF OF CONCEPT**: 2050

» **EXPECTED YEAR FOR MASS-SCALING**: 2060

» **IMPACT (1-10)**: 5.5

» **AUDACITY (1-10)**: 7.5

OUTCOME

A method to move the brain—with or without the entire head—of one person to the body of another, or to a non-human vessel, for over a year, while maintaining conscious thought or (in the case of cryonics) demonstrating that consciousness can be recovered after a time.

WHY THE NEED?

A successful brain- or head-transplant, from an old donor to the body (cloned or otherwise) of a young human being or to a non-human vessel, can potentially circumvent many of the mechanisms of aging. While the technique may sound ghoulish, it may be no more absurd than any organ transplant conducted in the present.

RELEVANT GRAND CHALLENGES

» Improving Treatment Tools

STIPULATIONS FOR A SUCCESSFUL BREAKTHROUGH SOLUTION

» The transplant procedure should be safe for the transferred brain

» The transplant procedure should be accessible— whether it relies on the availability of a recipient body, or if the detached consciousness is carried forward through a non-human vessel

» Avoiding rejection of the transplanted head or brain by the recipient's body

PROMISING TECHNOLOGIES FOR SOLUTIONS

Head and brain transplants seem to be the most likely technological solutions for this breakthrough. While such procedures seem grotesque to many, they have the potential to keep older adults alive for a time—possibly just enough time for new medications to be developed.

Conclusion

In this section we've covered 12 possible breakthrough solutions to overcome the grand challenges of longevity. These breakthroughs were developed in collaboration with a multidisciplinary community of global experts.

As stated at the beginning of this section, the list of breakthroughs included herein is not meant to be exhaustive. Great ideas abound. In the next section we highlight several additional breakthrough solutions that were generated from a unique two-day in-person gathering at the XPRIZE headquarters.

07.

BREAKTHROUGH SOLUTIONS FROM THE FUTURE OF LONGEVITY LAB

07

Introduction

IN THIS REPORT we have reviewed both the obstacles and remedies in the field of longevity, and synthesized that analysis into the grand challenges of longevity. Through this process we arrived at 12 breakthrough solutions that could help overcome the grand challenges.

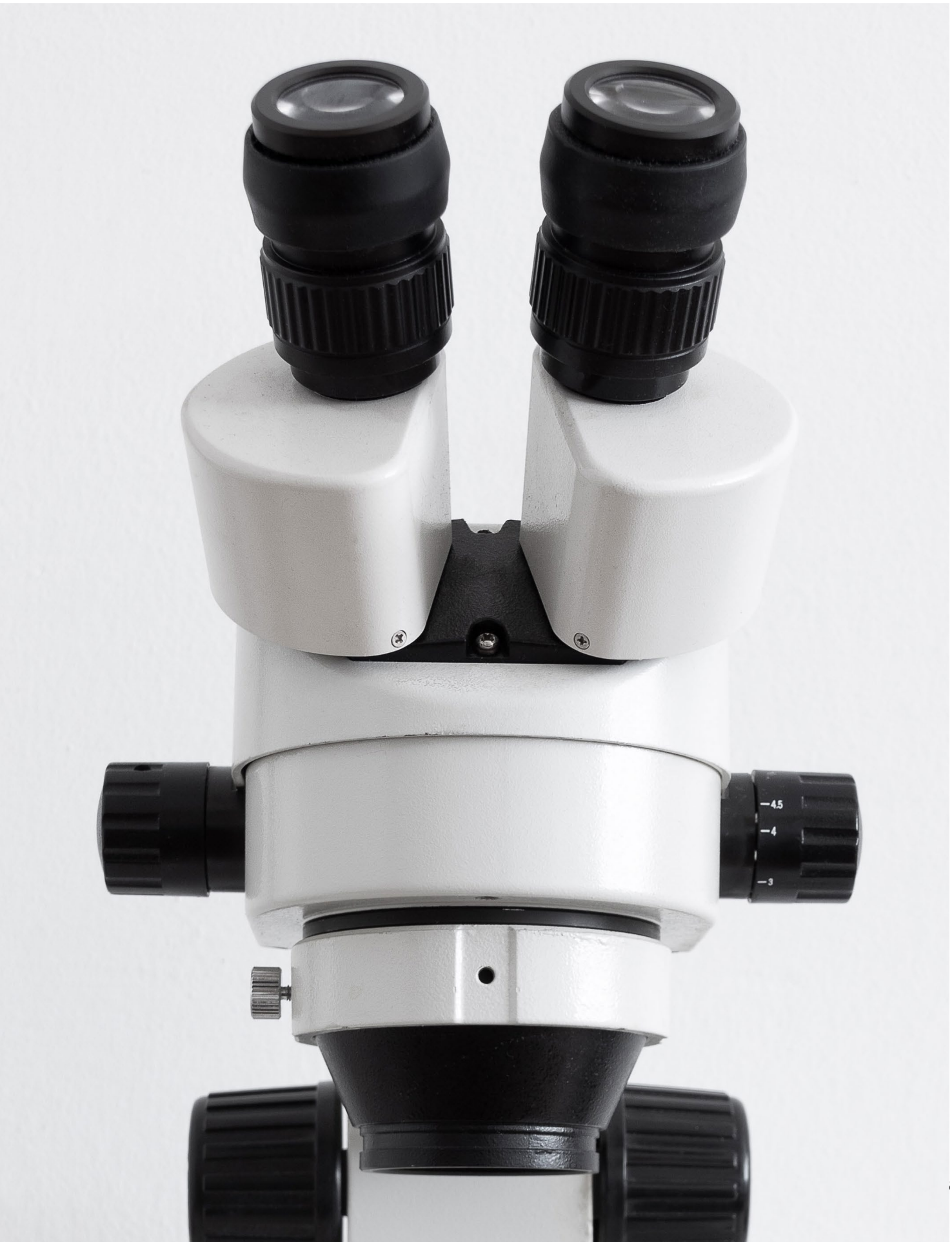
We recognize that our research process has inherent limitations and biases. That is why we have involved a vast expert community in the Future of Longevity Impact Roadmap research from the beginning.

In this section we review the outcomes of this energizing gathering. The breakthrough solutions and ideas for competitions have been revised and edited for clarity, and to fit with XPRIZE's goals and prize structure.

EXPERTS TOOK PART IN THE RESEARCH IN TWO MAIN WAYS:

» An active online community comprised of longevity and life extension experts, as well as medical doctors, futurists, economists, and others with relevant fields of expertise.

» An in-person, two-day Future of Longevity Lab at XPRIZE headquarters with 69 multidisciplinary experts, during which we reviewed the obstacles, remedies, grand challenges and the preliminary Breakthrough solutions we had developed. At the workshop we received insights from the experts on how to improve our analysis to date, as well as ideas for new ways to address aging and possible XPRIZE competitions.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From the Experts: Additional Ideas for Addressing Aging

Games for Good:

Gamification of Open-Source Operomics Solutions

OUTCOME

A SYSTEM THAT will collect "operomics"—the data pertaining to molecular analysis of DNA, RNA and proteins—from people. The system will use gamification elements to encourage people to voluntarily (and even eagerly) donate their data for research purposes.

RELEVANT GRAND CHALLENGES

» Advancing Scientific Understanding of the Aging Process

» Expediting Drug Development and Approval Processes

» Raising Public Awareness and Improving Public Perception

IMPACT

A system that collects cell and tissue data from people and shares it for research purposes could help accelerate drug development, as new promising drug candidates and targets could be discovered by analyzing the massive amount of standardized data. The data gathered may also facilitate the formulation of a robust theory of aging.

RELEVANT TECHNOLOGIES AND TECHNIQUES

» Sensors

» DNA sequencing

» Gamification

» Epigenetic mapping

» Proteomic mapping

FROM THE EXPERTS: Additional Ideas for Addressing Aging

Restoring the Self:

Demonstration of Reversal of Dementia Symptoms

OUTCOME

DEMENTIA WOULD BE reversed in older adults, in a trial with clear success criteria.

> "Dementia is the most damaging disease to society and the poster disease for the aging population."
>
> **KEITH COMITO,**
> PRESIDENT OF LIFE EXTENSION ADVOCACY FOUNDATION

RELEVANT GRAND CHALLENGES

- Expediting Drug Development and Approval Processes
- Raising Public Awareness and Improving Public Perception

IMPACT

Reversing dementia would have profound personal, societal and economic effects. Additionally, the ability to overcome a disease that is perceived almost exclusively as an aging-related one would likely stimulate an increase in public awareness of longevity studies.

RELEVANT TECHNOLOGIES AND TECHNIQUES

- Crowdsourcing (for funding and data collection)
- Open source (for data sharing)

Aging, Visualized:

High-Fidelity Visualization of Aging Outcomes

OUTCOME

A SERVICE THAT would combine data from several different sources (e.g., MRI scans, lab tests, epigenetic age markers, lifestyle questionnaires, activity tracking, etc.) to visualize projected aging outcomes for individuals.

RELEVANT GRAND CHALLENGES

- Advancing Scientific Understanding of the Aging Process
- Expediting Drug Development and Approval Processes
- Raising Public Awareness and Improving Public Perception

IMPACT

Such a service would help accelerate drug development by showing the effects that certain drugs and other external factors would have on an individual's aging process—which would likely encourage further participation in clinical trials. The data collected could also aid in developing a more robust theory of aging, and increasing public awareness of the aging process. Finally, if the system were capable of providing people with real-time information about their health, it could help people become more aware of how they are biologically aging and encourage healthier lifestyle choices.

RELEVANT TECHNOLOGIES AND TECHNIQUES

- Sensors
- Crowdsourcing (for funding and data collection)
- Open source (for data sharing)
- Personalization of treatments
- Epigenetic mapping
- DNA sequencing

"99% of the reason we need to do trials and experiments is because of the things we don't know about how the body works."

DR. AUBREY DE GREY,
WRITER AND CHIEF SCIENCE OFFICER OF SENS RESEARCH FOUNDATION

FROM THE EXPERTS: Additional Ideas for Addressing Aging

Gamifying Health:

Individualized Play to Motivate Better Health Outcomes

OUTCOME

BY USING TECHNOLOGIES like virtual, augmented and holographic realities, together with gamification elements, users would be able to experience multiple potential futures for their bodies and minds, in a way that will motivate them to create a better future for themselves.

RELEVANT GRAND CHALLENGES

- Improving Treatment Tools
- Raising Public Awareness and Improving Public Perception
- Ensuring Accessibility of Treatments

IMPACT

Many longevity treatments rely on a user's motivation and adherence to the prescribed lifestyle, diet and/or activity. As many people lack the willpower to maintain healthy habits, a tool that could enhance intrinsic motivation to do so could have impressive effects on their healthspan. It could, for example, bring to many the benefits of caloric restriction and physical exercise or, at the very least, healthier and more balanced diets.

RELEVANT TECHNOLOGIES AND TECHNIQUES

- Sensors
- 5G internet (for data sharing)
- Crowdsourcing (for funding and data collection)
- Open source (for data sharing)
- Personalization of treatments
- Gamification
- Virtual reality
- Holographic displays
- Citizen science
- Social robotics

Bio-Aging Tracker

OUTCOME

A DEVICE FOR people to measure their own biological age, the pace at which they are aging and the relevance to their health. The device would have an interconnected interface for people to share their data and compare it to others, and it would provide advice for actions they can take to improve their health and slow down their aging process.

RELEVANT GRAND CHALLENGES

- Advancing Scientific Understanding of the Aging Process
- Improving Treatment Tools
- Expediting Drug Development and Approval Processes
- Raising Public Awareness and Improving Public Perception
- Ensuring Accessibility of Treatments

IMPACT

A bio-aging tracker would increase public awareness of the aging process, and provide personalized consultation to every individual, thus helping increase accessibility of effective treatments. The collected and shared data could help accelerate drug development and approval processes, and would contribute to the eventual development of a robust theory of aging. Finally, as people become more aware of their health, they would be able to take better care of themselves, thus postponing the emergence of aging-related diseases.

RELEVANT TECHNOLOGIES AND TECHNIQUES

- Sensors
- 5G internet (for data sharing)
- Crowdsourcing (for funding and data collection)
- Open source (for data sharing)
- Personalization of treatments
- Gamification
- Citizen science

> "A critical tool to promote healthy aging and eventually reverse aging is to objectively measure aging."
>
> **DR. STEVE HORVATH,**
> PROFESSOR OF HUMAN GENETICS AND BIOSTATISTICS

From the Experts: Ideas for Future XPRIZE Competitions

FROM THE EXPERTS: Ideas for Future XPRIZE Competitions

Generation and Storage of Human Organs

THE CHALLENGE

THERE IS AN acute shortage of replacement organs for individuals. Furthermore, transplant rejection is a significant problem.

OUTCOME OF COMPETITION

» Organogenesis of personalized replacement organs for human beings

» The manufactured organs would be generated from the patient's own cells, or from cells that do not invoke rejection from the transplantee's immune system

» The organs would be capable of performing their normal tasks in the human body; a lab-generated heart should pump blood successfully in the body, while a lab-generated kidney would function well enough to make dialysis unnecessary

TECHNICAL DETAILS

The competition would last five years, with a prize of $20 million.

Longevity Peace Prize

THE CHALLENGE

THIS COMPETITION IS meant to disrupt societal acceptance of aging as the norm, and reprogram people's thinking that humans have to age (and die). Such narratives are pervasive in human culture, for various reasons, and affect legislation and regulatory agencies.

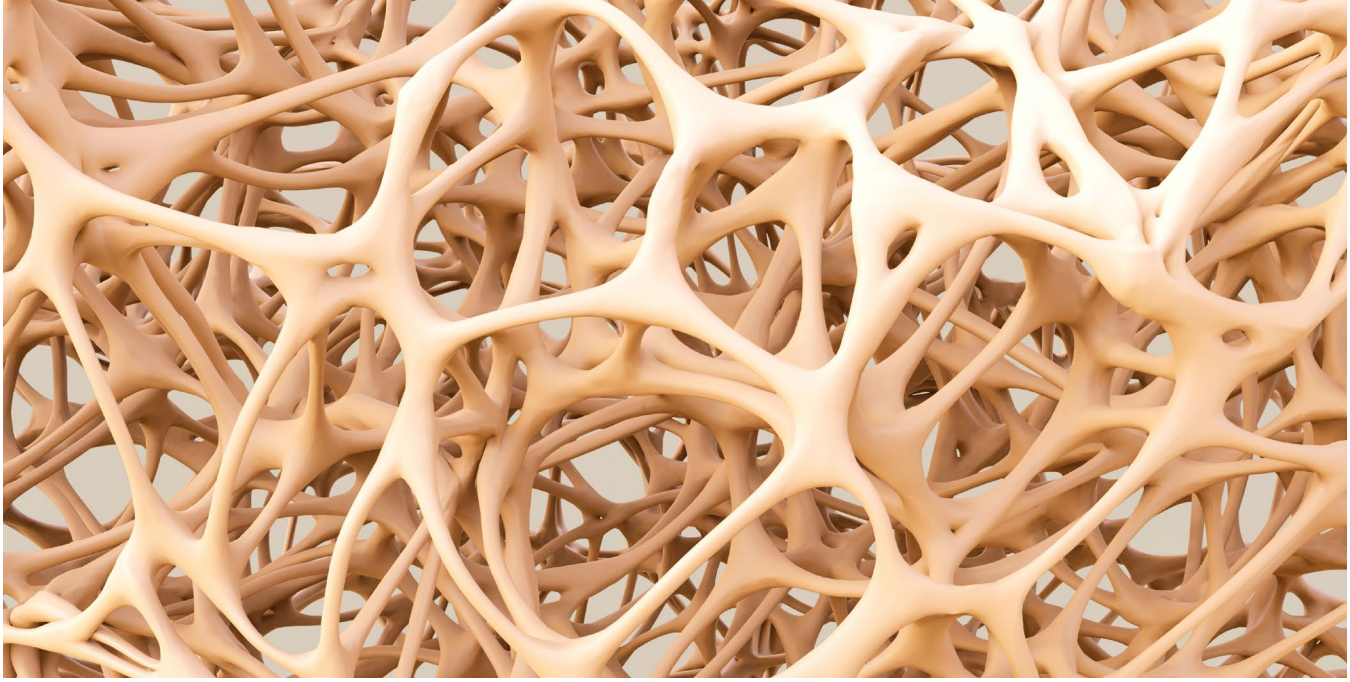
OUTCOME OF COMPETITION

» New laws and regulations that support people's right to adapt and engineer their bodies as they like

» Regulatory agencies acknowledging aging as a disease or a medical condition

TECHNICAL DETAILS

The competition would last five years, with a prize of $5 million.



FROM THE EXPERTS: Ideas for Future XPRIZE Competitions

Restoration of Tissue Regeneration Capabilities

THE CHALLENGE

THERE IS A need to prevent the loss of tissue regeneration capacity, which is associated with aging.

OUTCOME OF COMPETITION

» The tissue repair and regeneration capacity found in young people will be restored in elderly people

» The treatment will be demonstrated by rejuvenating the body's capability to handle one toxic condition (e.g., following alcohol consumption)

TECHNICAL DETAILS

The competition would last ten years, with a prize of $10 million.

Meaningful Reversal of Dementia

THE CHALLENGE

DEMENTIA POSES A critical challenge for society in economic, social, and personal ways. It is perceived by the public as one of the core symptoms of aging, but cannot be efficiently treated at present. Therapies arising from our existing understanding of dementia have failed for decades. Thus, an inducement prize would inspire needed new approaches to treating the condition.

OUTCOME OF COMPETITION

- Reversal of the dementia phenotype with clearly defined success metrics (physiological, cognition, etc.)
- The reversal would be demonstrated on a sufficiently large cohort of patients whose symptoms of dementia would be lessened

TECHNICAL DETAILS

The competition would last 10 years, with a prize of $20 million.

FROM THE EXPERTS: Ideas for Future XPRIZE Competitions

Forever 21

THE CHALLENGE

THE CHALLENGE IS to find a safe intervention that rejuvenates a human by 5-10 years of age. This competition would strive to overcome the reality that humanity is arguably not trying as hard as it should to develop rejuvenation medicines, given the amount of human suffering that could be alleviated and the potential benefit to the economy that a cure for aging would provide.

OUTCOME OF COMPETITION

- Rejuvenation by 5-10 years of age
- The treatment must last no more than one year
- The measurement would be conducted on four cohorts: 50-, 60-, 70- and 80-year-olds; each cohort would include around 200 participants
- Rejuvenation would be measured according to several different biomarkers and aging clocks

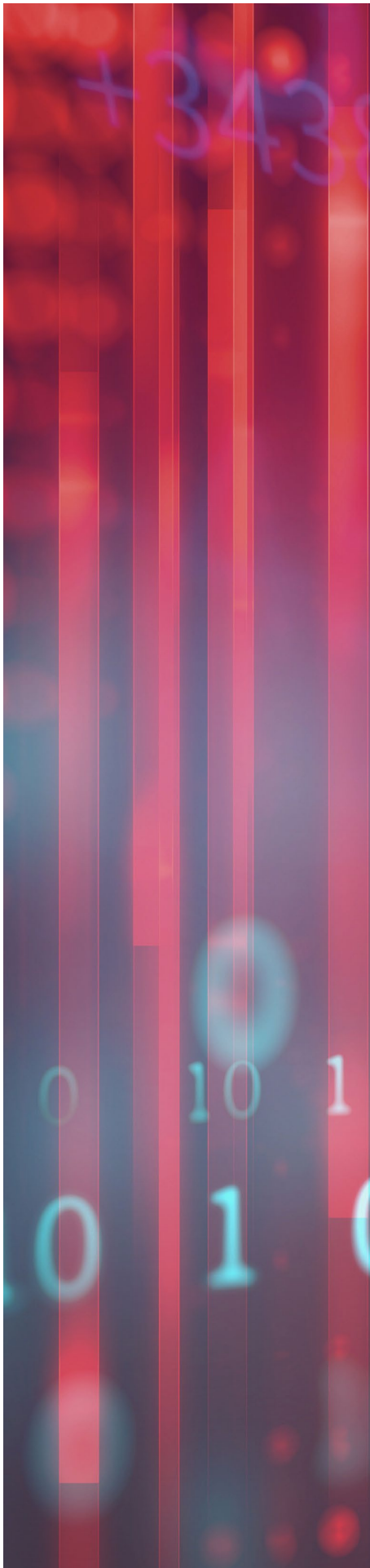
TECHNICAL DETAILS

The competition would last 10 years, with a prize of $100 million.

Conclusion

In these last two sections we've presented various solutions to address aging and ideas for future XPRIZE competitions that could contribute to a future of abundant longevity.

In the next section we'll demonstrate how the breakthrough solutions from the last two sections could come together to create a better future for us all, and what might await us if they don't.



08.

ENVISIONING THE FUTURE

08

Introduction

Scenarios for the Year 2040

Introduction

IN THIS REPORT, we've described the grand challenges standing in the way of a future of healthy longevity for all. We've also highlighted several breakthroughs that have the potential to overcome those grand challenges. In this section we will show how these breakthroughs could transform the present and how the future may change as a result of their implementation.

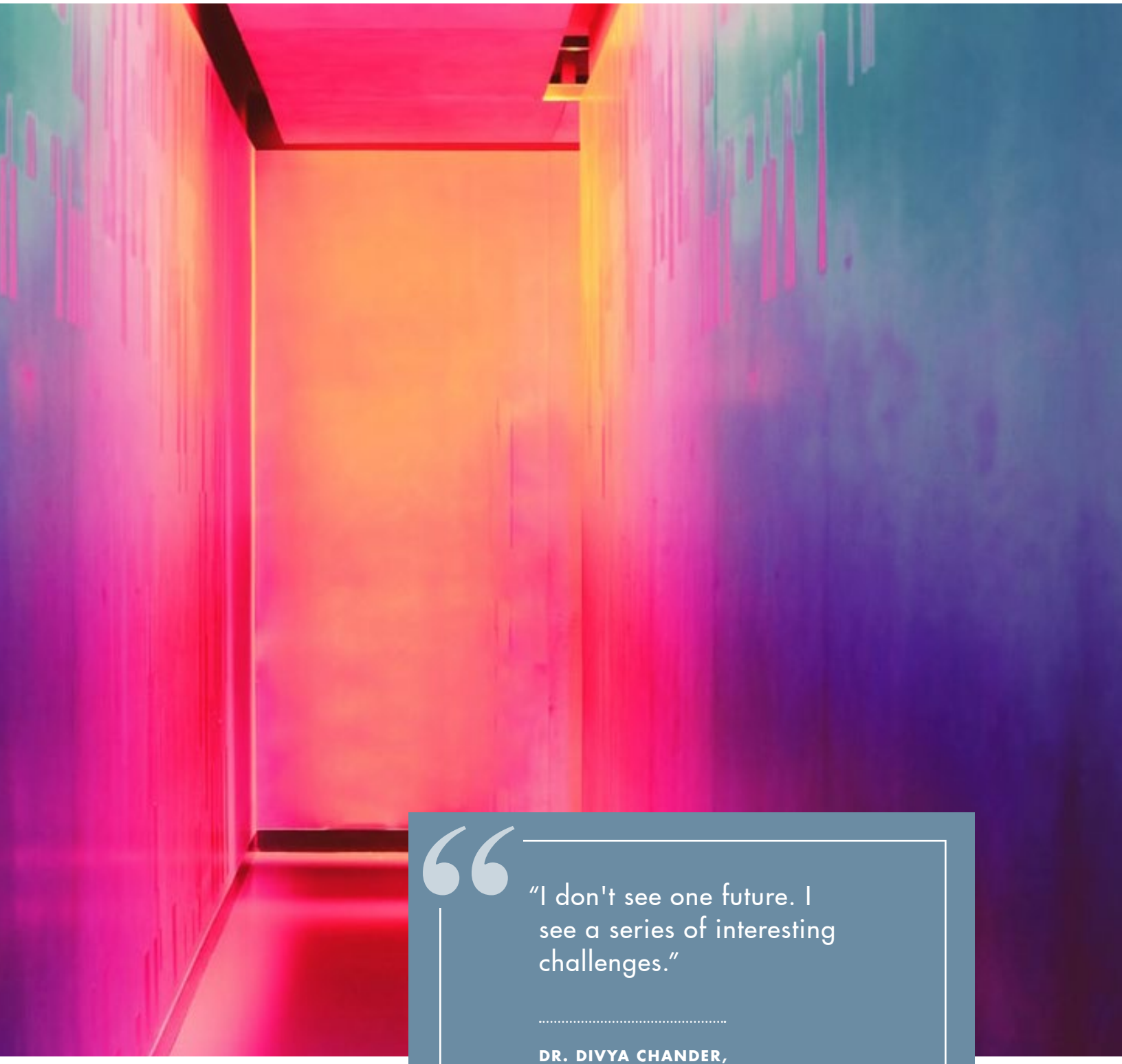
Unlike the past and the present, we lack data about the future. We therefore must rely on different tools to help us make sense of what lies ahead. To this end, we use *scenarios*.

Each scenario begins with a Set-Up—a bulleted description of the circumstances related to longevity in the year 2040. From there we move into a first-hand narrative of someone living in that future, which we call a *snapshot*. We conclude each scenario with an account of how that future scenario came to be.

We cover four distinct future scenarios—dystopian, business-as-usual, incremental, and transformative—each of which is plausible in its own way. These scenarios offer a relatable glimpse of how longevity-related trends may converge with other global trends to impact society. Each scenario deliberately has a varying degree of optimism. The intention for making them so is to consider both positive and negative outcomes of the measures that are taken or not taken today and in the near future. We start with the darkest and progress into the lighter outcomes.

Each scenario contains a different mixture of grand challenges that have gone unheeded as well as certain breakthroughs that have helped to drive progress. We set our scenarios 20 years in the future to keep them close enough for understanding what may be possible, yet far enough away so that the possibilities have substantial range.

While none of the provided scenarios will be fulfilled precisely as described, they teach us about what **COULD BE** so that we can better shape what **WILL BE.**



> "I don't see one future. I see a series of interesting challenges."
>
> **DR. DIVYA CHANDER,**
> PHYSICIAN AND NEUROSCIENTIST

THE COLLAPSED FUTURE:
Total Stagnation

SET-UP

▶ The global elderly population has more than doubled in proportion, with massive negative implications to society and infrastructure.

▶ Attempts to provide adequate healthcare and housing to the aging population have failed miserably. Many insurance companies have gone bankrupt.

▶ Few people believe in the concept of healthy life extension or age-reversal.

▶ The scientific foundations necessary for achieving longevity breakthroughs are not yet successfully laid or accepted.

▶ Governments refuse to accept aging as a treatable condition, or fund research in the field in any significant way.

▶ Pharmaceutical firms generally ignore research and development in the field of life extension and age-reversal.

▶ Most aging-related diseases, including cancer, Alzheimer's, and recently discovered illnesses, remain without a cure.

SNAPSHOT ACT I

There's nothing worse than hearing your father has Alzheimer's. The doctor gave me the diagnosis, said he was sorry—the routine disclaimer—and dismissed me. On the way out of the clinic, I pass a row of old folks, waiting their turn. Their clothes are torn and shoddy; they probably can't afford replacements. Some are with relatives, looking just as haggard and worn.

"We have to help him," I whisper to my wife that evening as we lay in bed. "And ourselves. We can't afford to keep him around if he can't contribute."

We turn to each other. She nods.

"You're going to pay Angel a visit?" she asks.

"Soon," I agree. "She took good care of Mom, and you know how important it is to support local businesses, the way the economy is doing right now."

She lays a comforting hand on my shoulder, then turns away, pulling on the blanket and leaving my feet out in the cold. I don't pull back. The kids are sleeping on her side of the bed tonight. Ever since we had to move into a single room apartment with Dad, that's how it's been.

At least Dad has stopped snoring—an odd benefit to the disease. I reach down and stroke his cheek gently. He mumbles and turns on the floor. I recall all the kindness and love he's shown me, all these years, and I silently promise that it won't be long now.

SNAPSHOT ACT II

Angel's neighborhood is far from affluent. Older people beg in the streets for food, clothes, comfort, love, or whatever else they might be missing. Some can barely walk, strewn on the pavement gasping for breath, clutching at the ankles of passersby. Others seem like ghosts and stare with scared wide-open eyes. Probably dementia.

I try to shake the despair from my head. The economic depression from five years ago was devastating. Many remain homeless. And as the prevalence of chronic diseases keeps increasing, the elderly are becoming more and more of a burden on society and their families. Only the wealthy can afford to keep their parents around now, let alone their grandparents.

That's where Angel comes in.

"We're currently running a discount on many of our best-sellers," she tells me, after the initial niceties and greetings. "Does your dad like the sea?"

I shake my head with a wry chuckle. "He and Mom were biologists on a navy ship, when they were young. He absolutely hated it."

"So, I guess the Final Departure Cruise is not for him," she concedes, looking through her catalog for other options. "Let's see. How about Flying to Heaven? We take them up high in the sky—it's a great view—there's gospel, and folk singers, too, so everybody is excited by the time the clouds start streaming into the cabin, and—"

I stop her. "Anything else?"

"Space: the Final Frontier," she says proudly. "For those who can afford it, we…" She glances meaningfully in my direction. I shake my head. She moves on. The options keep coming. Eventually, we decide in favor of merciful efficiency. We'll do it at home, but with a personalized touch.

Dad has always loved surprise parties.

SNAPSHOT ACT III

The party went great. Better than I could ever have anticipated. Dad came back home from one of his daily strolls—supervised by my three children (it's the only way he's been allowing us to get away with monitoring him)—and found everyone waiting inside, just for him. We had pretzels and vodka, linen on the table, and music playing, just like in the good old days. Dad was more responsive than he'd been over the past few months, smiling and joking with us. It felt like he was almost back. For a moment, I wanted to call the whole thing off. But I knew we had to do it. Just as we'd rehearsed, we told him to cover his eyes, and began to bind him up. That's when he started screaming.

Fortunately, Angel had prepared us for this. "It's an unfortunate fact of life," she said. "Nobody in their right mind wants to die. And even when they're not in their right mind, they still struggle against the final act."

We know we did the right thing. It would be impossible to keep looking after Dad at such an advanced age, especially with the dementia. Nobody did that kind of thing anymore. I wish things were different, but how could they be? We live in a world where old age is a curse, and nobody can do anything to break it. As I held him down, I promised to myself that when my time comes, I will go gently into that good night.

Dad fought back, but not for long. He's not as strong as he once was, and the spiked vodka definitely helped. The hired doctor came from behind with the anesthesia, and the rest was pretty routine, just like it had been with Mom. When it was over, I bent down, kissed his wrinkled brow, and closed his eyes. I could swear there was a look of gratitude on his face. We helped save him—and all the people he loved—from himself.

I feel grateful, too. It's all over.

HOW DID WE GET HERE?

It is difficult—if not impossible—to distinguish one main reason why things turned out this way. Indeed, several challenges went unmet. First and foremost, neither the public, politicians, nor governments could be convinced about the potential for life extension and age-reversal. Life expectancy in the United States began to decline in 2016, and politicians—trying to avoid blame and prioritizing the short-term—disparaged the idea that human beings could (or should) live for much longer than they do today. Whether from the media or from leaders of major religions, the masses heard the same message: "Be content with the life you have now, and the death you will have later. There is no other choice."

The elderly population continued to grow worldwide, and governments had to shoulder the burden of taking care of them. Many of the elderly—bedeviled with chronic illnesses and frailty—could not contribute to the economy. Even healthier older adults were largely driven out of the job market because of ongoing biases against the elderly and antiquated pension laws.

The economy couldn't support the large number of pensioners and chronically-ill older adults. In addition to having their wages garnished, young people became increasingly frustrated at the difficulty of marrying and supporting a family of one's own, as many of them needed to take care of their parents and grandparents. Inevitably, an economic depression dawned on the world, as people's consumption decreased so that they could focus only on the bare necessities of life—for themselves and for their loved ones.

In this state of economic depression, the elderly became societal outcasts. If you were old, chances were high that your children and grandchildren would cut their connections with you—whether because of the new zeitgeist, or to avoid the necessity of having to support you. In this grim reality, many older adults decided to commit suicide to prevent financially ruining their families. Many others found themselves in the street, driven from their homes and families as soon as they developed the first signs of some chronic illness.

As the number of homeless elderly continued to rise, tent cities and ghettos

became more commonplace in every large city. Many began resorting to begging, petty crimes, and even selling parts of their bodies for money, drugs, and—for those who actually wish to live longer in this grim environment—medication.

As the public disregarded the promise of life extension, there was less pressure on governments to support and promote longevity research. Funding was instead directed at new ways to keep sick people alive longer, despite the "smoldering" chronic state of illness in which it kept old people suffering. Instead of focusing on stopping aging itself, it was simply good enough to keep old people alive longer—regardless of their poor state of health.

Despite the lack of funding and the generally negative view of the concept of life extension, a few stalwart researchers were not willing to let go of the dream of the fountain of youth. Unfortunately, as research budgets shrunk, it became nearly impossible to develop significant discoveries. Breakthroughs in our understanding of aging—which could have led to the development of a robust theory of aging—were not achieved. Demonstrations of treatments on lab animals that proved aging could be halted, or even reversed, either went unpublished or were ignored and ridiculed by mainstream media.

Initially, pharmaceutical companies had high hopes for longevity treatments. However, as governments refused to recognize aging as a treatable condition, firms realized they would be developing a cure for a disease that does not officially exist, and which has no market potential. No medical doctor would've been legally allowed to prescribe this sort of treatment to their patients. And so, the industry went back to focusing on reactive drugs and treatments for aging-related diseases, rather than moving upstream and going after aging itself. As a result, reforms for real preventative healthcare laid dormant, and medical researchers and physicians were forced to contend with fixing the symptoms of aging, rather than addressing its root causes.

ASSESSMENT

Aging in 2040 is difficult, fraught with hardships, and bitterly inevitable. Perhaps worst of all is the despair that has overtaken the world. The elderly have no hope or desire for their continued existence. Their children face significant hardship. Young people have grown to despise their elders, even while knowing that they too will suffer the same fate. They feel powerless to change anything.

Even still, all hope is not lost. Indeed, change may be just beyond the horizon. Leaps in knowledge of the aging process may yet emerge, along with corresponding treatments following soon after such a breakthrough. The societal and governmental focus could shift to fighting aging itself. Such paradigm shifts are not unheard of, and once they are catalyzed, can sweep across nations at lightning speed. Then, people will again have hope for a dignified, long life. But in the meantime, countless lives are lost to the consequences of aging. All that the few remaining believers in life extension can do for now is keep their faith, even in a world that rejects the possibility of—or the need for—longevity.

BUSINESS AS USUAL:

Hope Is the Thing that Requires Having a Good Theory

SET-UP

▶ As the growing elderly population has highlighted the need for increasing healthspan, the public has become more aware and optimistic about the possibilities of life extension and even age-reversal in the future.

▶ Early longevity treatments are ineffective at best or act as placebos at worst.

▶ Disagreement among the scientific and longevity community, however, has led to difficulties in achieving a standard set of aging biomarkers.

▶ No robust theory of aging has been conceived, and thus there is no holistic understanding of the aging process.

SNAPSHOT ACT I

There's nothing worse than watching your husband have a heart attack. Trust me. I was there when his left arm started throbbing and I saw him collapse in agony. A day later, I'm sitting by his hospital bed with our son as we hear the doctor's report: the attack was almost fatal. My husband's heart is severely damaged. And he has about a month left to live.

"This is…" my husband grasps for the words, "… disheartening to hear!"

We all groan, our little family's routine right on cue. Then he gets serious.

"So what's it going to be, doc?" he asks.

The doctor gets straight to the point.

"We can't do much," he says. "Your other medical conditions prevent us from conducting surgery, and a heart transplant is out of the question. I'm afraid we can only offer some superficial treatments: helping you deal with the pain, mostly. But not much else."

We thank him—what else could you do?—but as soon as the doctor goes away, my hubby turns to me.

"Do you think you could do some research of your own?" he asks. "We keep hearing about all these treatments that supposedly extend life. Maybe it's about time to use one."

I nod. We both worked in the biotech industry, so we have some connections. Our son is well on his way to earning his biomedical degree as well, but I know I'll be the one talking with the researchers. Our boy is great and wicked smart, but he loves his dad too much. He just… doesn't have the heart to make tough decisions.

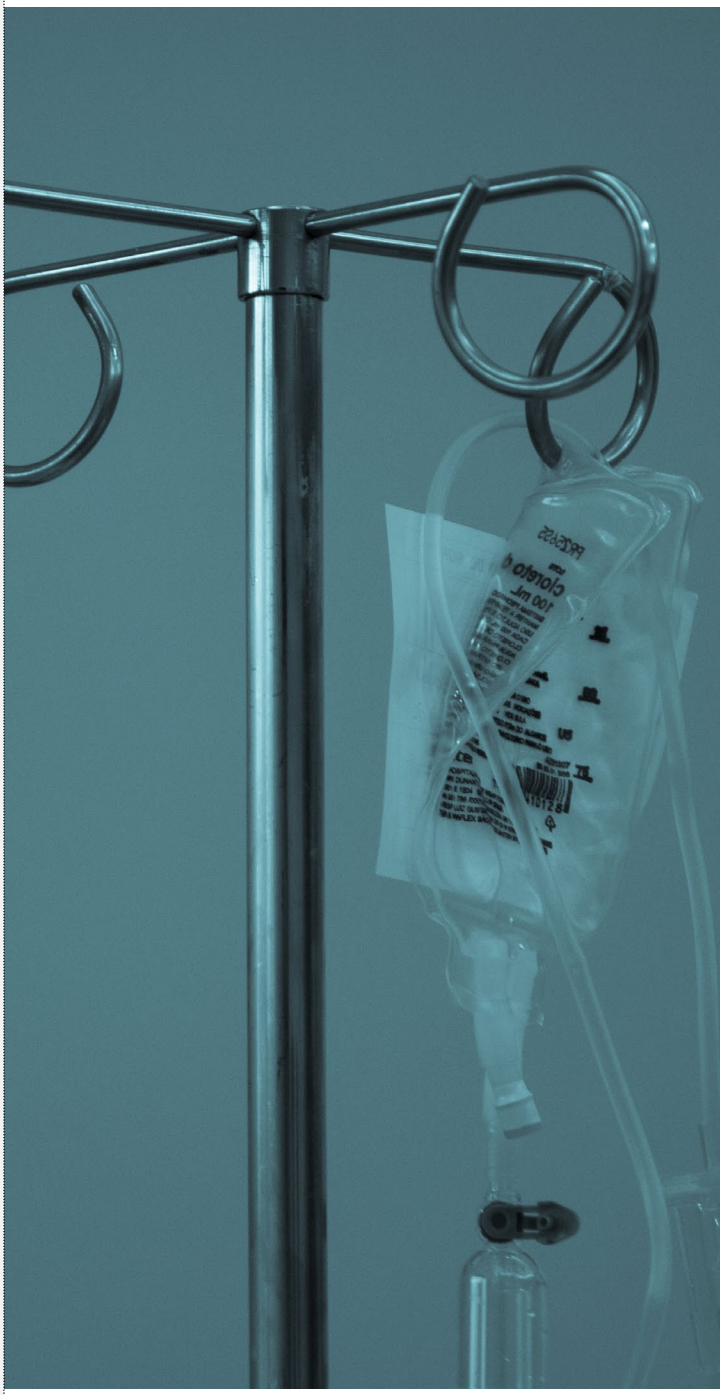
I reach out to my former colleagues. But things go downhill fast. They tell me about their work in the labs and make it clear that treatments will likely not be ready for clinical trials for at least another decade. They are all extremely professional, until I start asking about the field as a whole. Then they digress to pointing out the flaws in each other's work, subtly at first, and then their criticisms become downright spiteful. None of them believe the others' results hold much promise.

A week later, while I'm visiting my husband in the hospital, he takes the disappointing news in stride and informs me that he's been doing his own research—when he's not too busy charming the nurses.

"The nurses gave me this guy's business card. He's that holo-display medical doctor, what's his face," he says in amusement. "You wouldn't believe the crazy stuff he's selling: anti-aging, things to cure your heart, all that. And nothing is scientifically verified, which of course makes his job so much easier. You want double-strength antioxidants? He's got `em. Triple-power ding-dongs to give your cells quadruple metabolic energy? Got that too. You want ancient Neanderthal rejuvenation rituals with a virgin goat's blood? Heck, he'll probably drag the goat to the altar himself, as long as you can pay the bill. He's got more treatment centers than I've got fingers and toes. He's a multi-millionaire, on all the holo-display channels as a medical consultant to the rich. A bona fide quack to the cuckoos."

I feel a smile slowly creep onto my face. This guy sounds perfect.

"I think," I muse aloud, "we're going to pay him a visit real soon."



SNAPSHOT ACT II

"So, what we have here, in our Longevity Inevitable: Foundation Earth—or LIFE, as we like to call it—is the cure for everything," says the holo-display scientist. "And I say that with all possible humility and skepticism. Neither of you needs to worry. We have the best treatments for you both."

"For us both?" I raise an eyebrow. "My husband is the one in critical condition."

He spreads his hands apologetically.

"Of course," he says. "Of course. But with the treatments we have, we can not only give him the chance to live much longer, but we can put a halt to *your* aging process as well."

"But how does it work?" I ask, then brace myself as I receive a monologue of pseudo-scientific gibberish. The only thing missing here is, indeed, a bleating goat. I see my husband stirring, preparing to deliver some tirade of his own about charlatans selling snake oil to desperate people. I step in.

"We'll take it!" I declare, ignoring my husband's startled gaze. "I want the best for my husband. Just tell us the cost, and we'll make the arrangements."

After much congratulations and another round of empty promises from the "doctor," we find ourselves outside the treatment center gate, heading home in our self-driving taxi. Hubby turns to me, confused and with as much fury as he can muster in his weakened state.

"Have you gone insane?" he demands. "Did you even see how much they charge for just a single week in that place? There's no way we're wasting money like that and for no good reason! You don't you actually believe that nutjob, do you?"

I hold a finger to his lips and ignore his feeble attempt to bite it. Then I point at my chest.

"See that?" I ask. "It's a recording device. Everything he just said—all the promises of health and longevity—has been recorded. Now, all we have to do is sign you up. He'll treat you the best he can, and when he fails… Well, that's when we'll submit the multi-million-dollar class-action lawsuit. We're going to be rich."

"You'll be rich," he points out. "I'll be dead."

Then he pauses and considers it. "But I'll be dead anyway. And you'll have enough money to go on, to support the family. And as a bonus, we'll take a charlatan out of business and prevent him from defrauding others." He pauses in thought again. "Did you actually plan all that?"

I nod and put my head on his chest to hide the tears welling up in my eyes. He holds me close, trembling, and whispers hoarsely in my ear the only words that still matter for the next month.

"I knew I married right."

HOW DID WE GET HERE?

The good news is that the longevity movements and campaigns succeeded in bringing about a bona-fide change in public opinion. Several high-profile campaigns in the 2020s convinced many people of the great strides scientists were making in the field of longevity. News of breakthroughs like demonstrating age-reversal in lab animals (mainly small vertebrates like mice and rats) continued to bring prominence to the field and boosted public optimism.

For the first time in humanity's history, people began to believe they may be able to enjoy treatments that maintain their youthfulness and extend their lifespan. Nobody had any clue about the efficacy of such treatments, but for the first time, widespread hope existed.

Unfortunately, that hope was offset by relentless disagreements within the scientific community. While research has advanced in the past decades, bringing more potential ways to quantify biological age, no one set of aging biomarkers has been sufficiently comprehensive to be accepted as the gold standard by the academy, industry and governmental authorities. Drug development slowed as a result, as researchers were required to consider multiple (sometimes contradictory) sets of aging biomarkers.

As scientists continued debating the basic aspects of aging, a robust theory of aging was, unsurprisingly, also slow in coming. A shared platform with data on older adults was expected to provide the information needed to enable such a theory, but delays in its implementation hindered scientific advancement.

And so, scientists and pharmaceutical firms trying to develop age-reversal and life extension drugs found themselves mainly working in the dark. Indeed, the few treatments developed for humans were highly inefficient. They provided mostly cosmetic benefits—slight tightening of the skin, a firmer gait—but systemic rejuvenation of the body has remained a distant dream.

Amid this hype-filled atmosphere, there's been a surge of citizen science being performed in the name of fighting aging. Many people inpatient with the current rate of medical progress choose to take their chances on "biohacking" different treatments. While most scientists and clinicians raise concern that these kinds of unproven therapies offer no actual benefit, and may even cause users more harm than good, some support and even capitalize on these methods.

ASSESSMENT

One of the most critical challenges is solved. The public is now aware of the approaching possibility of halting aging. Unfortunately, governments, the pharmaceutical industry, and the scientific community have failed to uncover the basic science underlying life extension and age-reversal. Research is sluggish, and robust theories and useful models for aging are nowhere in sight.

That said, not all hope is lost. The public's enthusiasm for the field and its implications promises that research into longevity will continue to be well-funded. As governments, the academy and industry settle on a single definition and theory of aging and its biomarkers, the field is sure to make a great leap forward—but much later than it could have.

THE INCREMENTAL FUTURE:

Longevity, A Luxury for the Few

SET-UP

▶ The public is generally excited about longevity prospects, thanks to a few successful clinical demonstrations of reversing aging in tissues in humans. These demonstrations reinvigorate funding to continue these innovations and discover new options for regenerating or growing whole organs in the lab.

▶ However, the most advanced treatments have yet to be approved by the regulators, delaying their release into the market.

▶ A small number of longevity treatments—the trials for which were drastically accelerated thanks to in-silico simulation—have made it to market. These treatments are of limited efficacy; they extend lifespan by less than ten years.

▶ Due to the scarcity of such treatments, drug providers can maintain wildly high prices, meaning they are inaccessible to most of the population.

▶ Governments are unwilling to subsidize existing treatments due to their limited impact on the conditions of aging.

SNAPSHOT ACT I

There's nothing worse than seeing the look in a patient's eyes when you have to tell them they've got cancer.

"At least tell me this, doctor," the patient says weakly. "Will I be able to play the violin after you remove the tumor?"

"I'm not sure if surgery is the best option at this stage," I tell him gently. "The cancer is extremely aggressive, and has spread to your—"

"But if we do the surgery," he persists, "will I be able to play the violin? Just tell me: yes or no."

I look helplessly at his wife. She nods her head.

"Yes," I relent. "Of course."

"Good," he whispers, and lets his head sink to the pillow. "I never could before."

His wife gives me an apologetic smile.

"I'm sorry about that," she whispers. "He's been waiting for years to make that joke."

I smile at her. It's good to see a patient keep his sense of humor, even when the news is spectacularly bad.

"I know surgery is extremely risky," she says. "We both have backgrounds in biotech, and I read the literature about this kind of tumor. Is there nothing else we can do?"

I hesitate.

"There is...one thing you may wish to try," I say reluctantly. I don't like selling my own merchandise. "In my lab, we're working on a new kind of treatment that's going into clinical trials right now. It's not specifically designed to hold back cancer, but its effects are more holistic in nature. It's... well, it's meant to halt aging, and has even shown some effects of age-reversal in lab animals. It may be that your husband's immune system will receive a boost from this drug, helping it fight the cancer. It's a slim chance, but we could give it a try. I can help you get into the clinical trials, if that's what you want."

They agree, of course.

A month later, he's already getting the treatment at full dose. I am not supposed to know that, what with double-blind experimental procedures, but the effects are unmistakable.

For one thing, his hair grew back, and it is jet black.

SNAPSHOT ACT II

"How are you doing?" I ask the patient as he enters my office.

"You know, doc," he says thoughtfully, "a few months ago, I tried to look up impotence on the internet, but—"

"But nothing came up," I finish for him, and he grins.

"Now I don't have to look it up anymore," he says confidently. "I'm fixed, doc. You fixed me on every level."

Looking at him, I can't help but agree. The experimental drug has done wonders on him. Out of all the patients, he is among those who have responded best to it. He's regained his lost muscle mass, and his former frailty is all but gone. Where once he had thin white hair, his head is now covered with a thick black shock. His wrinkles and liver spots have all but disappeared. The cancer is in full retreat. And his virility, well, we haven't tested for that, but he's already made it quite clear. And his wife seems happier, though that, I assume, is probably due more to his cancer being in remission.

There is just one problem.

"I asked you here because I have some news," I tell him. "Very… good news, I think. Early data is suggest that the drug appears to be a success. The clinical trials are now drawing to an end, and we'll have to conclude the procedures this week."

He watches me carefully. "And the bad news?"

"I didn't say there was any bad news—"

I stop and sigh. No point beating around the bush.

"The bad news is that, starting this week, we won't be able to treat you any longer."

A sharp intake of air, and then, quietly, he asks, "So what will happen to me?"

"We will keep treating your cancer with the best drugs your insurance can subsidize, and—"

"Cut the crap, doc," he stops me. "What's going to happen?"

"We don't know," I admit. "It'll take around two or three years, maybe longer, until the pharma firm I'm working with analyzes the results and gets FDA approval for the drug. If…if they even do so."

I didn't dare say anything beyond that. The drug is working so well, so incredibly well, that the higher-ups surely realize it is prone to revolutionize the entire healthcare industry. And along the way, it will likely disrupt all the other drugs the company—and the industry—have on the market that keep diabetes, or heart disease, or strokes, or whatever in check. I have my concerns that the firm and its competitors will decide to wait, choose to squeeze the most profit out of their current drugs, before moving on to the next golden goose. It won't be a long wait—just a few years, probably. But for my patient here, and many like him, that will be too late.

"If I stop taking the drug," he says, "the cancer will come back."

It wasn't a question, but I answer him anyway.

"We don't know," I repeat.

"I'm going to die," he says somberly. "I'm going to die, because of bureaucracy and some CEO wanting yet another yacht. Come on, doc, you know that."

"Please," I say, "We… I—"

My words die in my throat. What can I possibly tell him? He's right. He will die, unless we can get him on a regimen of drug injections, at least once a month. But where can he get the drug from? I can't give him an unapproved drug, outside of clinical trials. If I did, and anyone were to find out, my career would be over, and I could lose everything.

"I can't help you," I said. I hurriedly added, "I can't give you any more of the medication. It's in that cabinet over there, in the lab, and that's where it'll stay, you understand?" I point at the small refrigerated cabinet. "It'll stay right there. It's not going anywhere. And you couldn't even inject it yourself without the specialized needles and syringes—and those are all staying in the lab, too, in the same cabinet."

He nods slowly, his eyes thoughtful. I rush on.

"You still have the code for the faculty door, and for the lab itself, right? Just… just in case we ask you to come in for further experimentation. Just don't come at night, okay? Especially tonight, because nobody's going to be there. We're going out, all of us, to celebrate the trial's end."

"Thank you, doc." He rises unsteadily to his feet and shakes my hand. At the door, he stops and turns back to me, the smile back on his lips.

"Maybe I'll have a celebration of my own tonight."

HOW DID WE GET HERE?

It all seemed to go well early on, back in the 2020s. A standard set of aging biomarkers was established, data collection and sharing systems were instituted and put to work, and the scientific community produced its first-ever unified theory of aging by the early 2030s.

Then the wheels of progress unexpectedly slowed. It turned out that understanding aging is much easier than actually preventing or reversing it. Ideas for treatments were abundant, but very few were actually taken up by the overcautious pharmaceutical industry. Of the few promising drug candidates that were sent to clinical trials, most did not make it through the approval process, which took an extraordinarily long time to conclude. Treatments that did make it through were rarely very effective, extending lifespan and disease-free periods by only a few years. Revolutionary treatments continued to face economic and political barriers.

As the few pharmaceutical firms that managed to bring their limited longevity treatments to market noticed the dearth of other effective options, they felt free to raise their prices. National social security institutions refused to provide subsidies, as governments could not justify spending vast sums of money on treatments that would scarcely if at all improve older adults' productivity. Longevity treatments thus were reserved only for those wealthy enough to afford them—usually the top 10% in developed nations' wealth distribution.

While the uninspiring development of longevity treatments is partly because of the still-early technological state of treatment tools, some of the blame also falls squarely on the shoulders of pharmaceutical firms and governments. The regulatory requirement to conduct expensive and long clinical trials, rife with bureaucratic and administrative tasks, made it nearly impossible for young innovators to make good on their promising ideas. Instead, they found it difficult to raise enough funding to test and demonstrate their ideas. Thus, the flow of innovations and new paradigms got nipped in the bud.

The large pharmaceutical firms, for their part, encouraged the regulators to maintain these burdensome policies. They understood that high costs for the development of every new drug would deter new entrants and strengthen their chokehold on the longevity field. The established firms thus lobbied governments and international organizations to maintain the onerous status quo. Their profits grew, even as the longevity field suffered.

ASSESSMENT

The basic scientific breakthroughs for longevity and age-reversal have all been laid out in this scenario, but the final stage—developing a set of effective and diverse treatments that could rapidly gain approval for use—has not been achieved. The regulators refused to budge on the requirements of clinical trials, and a few large pharmaceutical firms maintained a monopoly on the longevity field, which stagnated progress. Together, these factors led to the emergence of an inefficient longevity market touting lackluster yet highly expensive treatments.

THE TRANSFORMATIVE FUTURE:
Aging, Overcome

SET-UP

▶ The longevity revolution is underway. On average, the onset of aging-related diseases and conditions has been postponed by decades.

▶ Young and audacious innovators are encouraged to take part in the innovation of scientific processes, and their ideas have clear paths to be rapidly translated into actual treatments.

▶ Treatments are thus accessible to nearly everyone, and governmental coffers receive a net gain from the savings of compressed morbidity.

▶ Powerful age-reversal and life extension treatments are available for pets and farm animals but should soon be translated for human use as well.

▶ New treatments can be tested quickly and effectively on in-silico and in-vitro models, dramatically accelerating the research and development and approval process.

▶ Maximum lifespan has moved to 130 years and new records are expected soon.

▶ The theoretical and basic scientific understanding of aging has been mostly achieved.

▶ Prices for currently available treatments remain low due to fierce competition between pharmaceutical firms and governments' willingness to provide subsidies for their elderly populations.

▶ Schools and universities cover curriculum about healthy aging and longevity science, and the public understands the great potential of longevity research and treatment.

SNAPSHOT ACT I

There's nothing worse than being told that you and your seventy-five-year-old wife have terminal cancer, but your cat is going to live forever. For starters, you feel offended. Really? The cat?

But then again, let's face it. Mr. Meow has always considered himself superior to us, or any human, really. You can see it in his eyes. Ever since he became the Immortal Mr. Meow, as we've taken to calling him, his attitude… Well, it remains exactly the same. Immortal or not, cats are cats.

We, on the other hand, are going to die. All things considered, we took the news reasonably well.

"He's going to take a leak over our graves," my wife says glumly, staring at the Immortal Mr. Meow over a late-night martini. "You know that, right?"

"Probably," I agree. "But maybe it's for the best. Do you know how immortal pets are being created today?"

She shakes her head.

"Genetic engineering," I utter the magic words. "Some crazy stuff those longevity scientists have come up with. Much better than what they have for humans right now. Basically, they re-engineered Mr. Meow's liver cells so that they now manufacture and secrete the age-reversal substance into his bloodstream. Some of it may even find its way into his urine, so…"

"He's going to turn us into zombies after we die." She drains her glass in one gulp.

"Well, probably not that. I haven't heard of any drug that can revive the dead. Not yet anyway. The age-reversal substance basically rejuvenates all the systems in the cat's body. It makes him young again, and provides protection from aging-related diseases, like dementia, heart disease or…" I meet her eyes. "Or cancer."

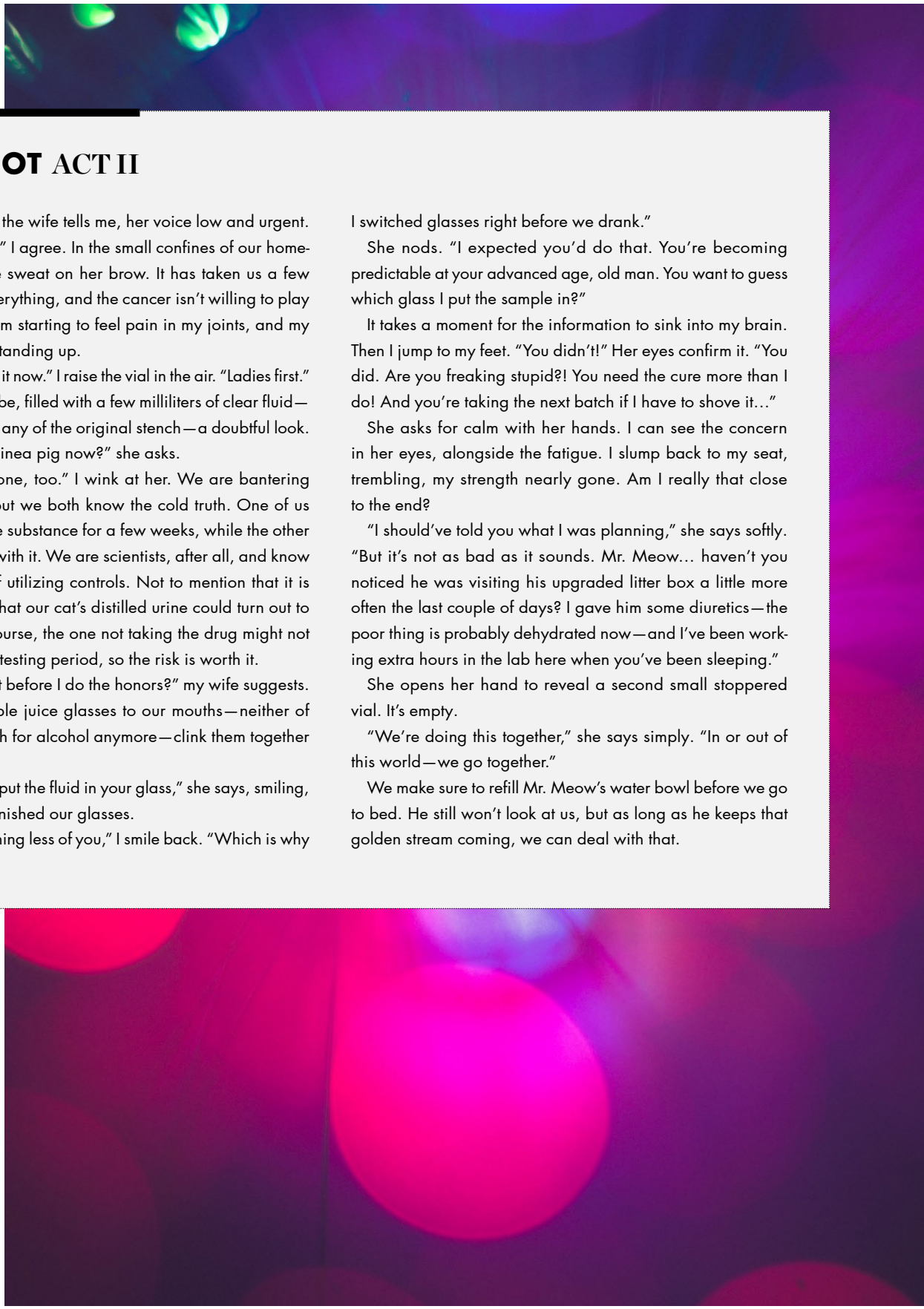
She opens her mouth, but I hurry on.

"And you know the best part?" The same substance that the cat's cells are producing is currently being tested in clinical trials on human beings. And I'm hearing good things about the early results."

"So, in… what, five to ten years…we'll get to enjoy the same level of treatment Mr. Meow gets right now?" Her mouth tightens. "You do realize that in our current condition, we're not going to last the year, right?"

I nod. That is, indeed, the problem. But we're both retired biotech engineers, the wife and I. Give us a problem for breakfast, and we'll produce distilled cat urine by lunchtime.

Which is exactly what we do. And Mr. Meow never forgave us this special indignity.



SNAPSHOT ACT II

"You're crazy," the wife tells me, her voice low and urgent.

"Crazy for you," I agree. In the small confines of our home-lab, I can see the sweat on her brow. It has taken us a few weeks to build everything, and the cancer isn't willing to play nice and wait. I am starting to feel pain in my joints, and my wife has trouble standing up.

"We need to do it now." I raise the vial in the air. "Ladies first."

She gives the tube, filled with a few milliliters of clear fluid—thankfully without any of the original stench—a doubtful look.

"So I'm your guinea pig now?" she asks.

"And a lovely one, too." I wink at her. We are bantering back and forth, but we both know the cold truth. One of us has to keep off the substance for a few weeks, while the other one experiments with it. We are scientists, after all, and know the importance of utilizing controls. Not to mention that it is entirely possible that our cat's distilled urine could turn out to be toxic. But of course, the one not taking the drug might not survive that early testing period, so the risk is worth it.

"One final toast before I do the honors?" my wife suggests. We raise our apple juice glasses to our mouths—neither of us has the stomach for alcohol anymore—clink them together and drain them.

"You do know I put the fluid in your glass," she says, smiling, once we'd both finished our glasses.

"I expected nothing less of you," I smile back. "Which is why I switched glasses right before we drank."

She nods. "I expected you'd do that. You're becoming predictable at your advanced age, old man. You want to guess which glass I put the sample in?"

It takes a moment for the information to sink into my brain. Then I jump to my feet. "You didn't!" Her eyes confirm it. "You did. Are you freaking stupid?! You need the cure more than I do! And you're taking the next batch if I have to shove it…"

She asks for calm with her hands. I can see the concern in her eyes, alongside the fatigue. I slump back to my seat, trembling, my strength nearly gone. Am I really that close to the end?

"I should've told you what I was planning," she says softly. "But it's not as bad as it sounds. Mr. Meow… haven't you noticed he was visiting his upgraded litter box a little more often the last couple of days? I gave him some diuretics—the poor thing is probably dehydrated now—and I've been working extra hours in the lab here when you've been sleeping."

She opens her hand to reveal a second small stoppered vial. It's empty.

"We're doing this together," she says simply. "In or out of this world—we go together."

We make sure to refill Mr. Meow's water bowl before we go to bed. He still won't look at us, but as long as he keeps that golden stream coming, we can deal with that.

SNAPSHOT ACT III

"So," my wife says.

"So," I agree. "Young again. Somewhere back in our thirties, I think."

"And healthy," she adds. "The doctor can't believe the results."

"Do you think there will be side effects from continuous use?" I ask.

"Almost certainly. But are they worse than the alternative?"

"Probably not," I allow. "But do you realize what this means?"

"Assuming that the substance works the same for everyone?" she asks. "Probably that humankind is going to experience some major social change. People will live longer and will be healthier. They will accumulate more experience, knowledge, and wisdom. Geniuses will take a very long time to die and will keep contributing their ideas to humanity throughout their lives. Of course, tyrants will also stay alive longer, but will they always retain their power? That's definitely a question we need to consi—"

I stop her.

"I mean, do you understand what it means, that you can obtain the substance from cat's urine, just like that, when there's still some five years or more before it officially hits the market?" I ask.

My wife sits up straight. One of the apparent side effects of the treatment is a renewed passion for adventure and fresh ideas. And we are both rather entrepreneurial.

"We… could help a lot of people," she says. "Right now."

"We could," I agree. "But we don't have enough cat urine for it."

We both turn to look at the Immortal Mr. Meow.

"I think," my wife says slowly, "it's time for Mr. Meow to find a missus."

Mr. Meow sees us looking at him, and begins inching his way out of the room. He's been doing his best of late to let us know he's feeling slighted.

"We'll need a lot of kittens with the same genetic makeup," I tell the wife. "Maybe we should think bigger. Mr. Meow is going to work extra-time with the ladies for the rest of his life. And that might be much longer than either one of us can imagine."

At the mention of his name he gives us one last reproachful look before he slinks out the door. Clearly, he isn't happy with us right now.

But in the end, there are worse fates for a cat. I think things turned out well for him.

HOW DID WE GET HERE?

Sometimes, it's the small things that make a difference. So it was in the case of "Mighty Mouse"—an old lab animal whose youth was restored via a combination of cutting-edge age-reversal treatments. Mighty Mouse, first revealed to the public in the early 2020s, has had many progressively longer-lived successors by 2040, and this has been a source of inspiration and hope for millions. Partly thanks to the consolidated efforts of properly educated medical journalists and politicians, the zeitgeist has shifted: people viscerally understand that it may indeed be possible to stand up to the grim reaper.

Mighty Mouse's appearance on the stage of history precipitated a resurgence of longevity advocacy. Public pressure pushed politicians to increase research budgets and encourage longevity-related research. Soon after, the first U.S. presidential candidate who openly supported longevity and age-reversal was voted into office. Other countries followed suit, and longevity became the new buzzword.

The world's youngest and brightest minds were attracted to the field of longevity, lured by the waves of funding and how much promises the field held for exponential development. They made use of the most advanced research tools available to humankind: from sophisticated AI engines that were used to produce novel hypotheses about the nature of aging, to futuristic imaging devices that could shed light on the ongoing affairs within the body, and even inside cells. Their work was bolstered by vast amounts of data about the aging process, obtained from the aging population via the omnipresent internet of things, and stored for research purposes on a shared database.

All the data, together with the insights provided by AI engines, was used to develop sophisticated in-silico and in-vitro models of the aging process. In light of such sophisticated research tools, it is no wonder that by 2030, less than a decade after Mighty Mouse captured the world's attention, a robust theory of aging was proposed and widely accepted by the research community.

Governments, meanwhile, accelerated the oncoming health revolution by redefining aging as a treatable condition. To meet the demand in a promising new market, the pharma industry swiftly began developing age-reversal and life extension treatments for human beings. The development of reliable biomarkers, a wide application of right-to-try laws, and thoughtful information management practices allowed for faster clinical trials and amplified the availability of relevant data. Longevity treatments were successfully demonstrated on farm animals and pets, which lent credence to their full potential.

By the year 2040, the results of several clinical trials for longevity drugs have started to become public knowledge. While not all drugs and treatments focus on the same pathways and aging mechanisms, they have an undeniable effect on the human body: some clean clogged arteries, others restore suppleness to aged skin, still others rejuvenate aging hair follicles and bring back some of the vigor of youth. Combinations of these drugs exhibit an even more powerful effect in clinical trials, which now can readily validate combinatorial therapies.

The effects these drugs have are not unlimited—they are almost certainly not the fabled final solution for aging—but they clearly provide a preliminary form of age-reversal.

ACCESSIBLE TREATMENTS FOR ALL

As the scientific foundation for our understanding of aging was publicly disseminated, pharmaceutical firms across the spectrum could compete with each other on producing longevity treatments. Prices of the early treatments started high but quickly decreased as a result of the competition. Furthermore, as those treatments had a practical function for the economy—reducing the incidence of aging-related diseases that prevented people from working and compressing morbidity that bloated healthcare spending—many governments were eager to subsidize them for the entire population. The cost of the treatments to national budgets was easily matched and even exceeded by the increase of productivity of older workers (helped along by the growth of the elder education industry) and the reduction in the number of chronic patients served by national healthcare systems.

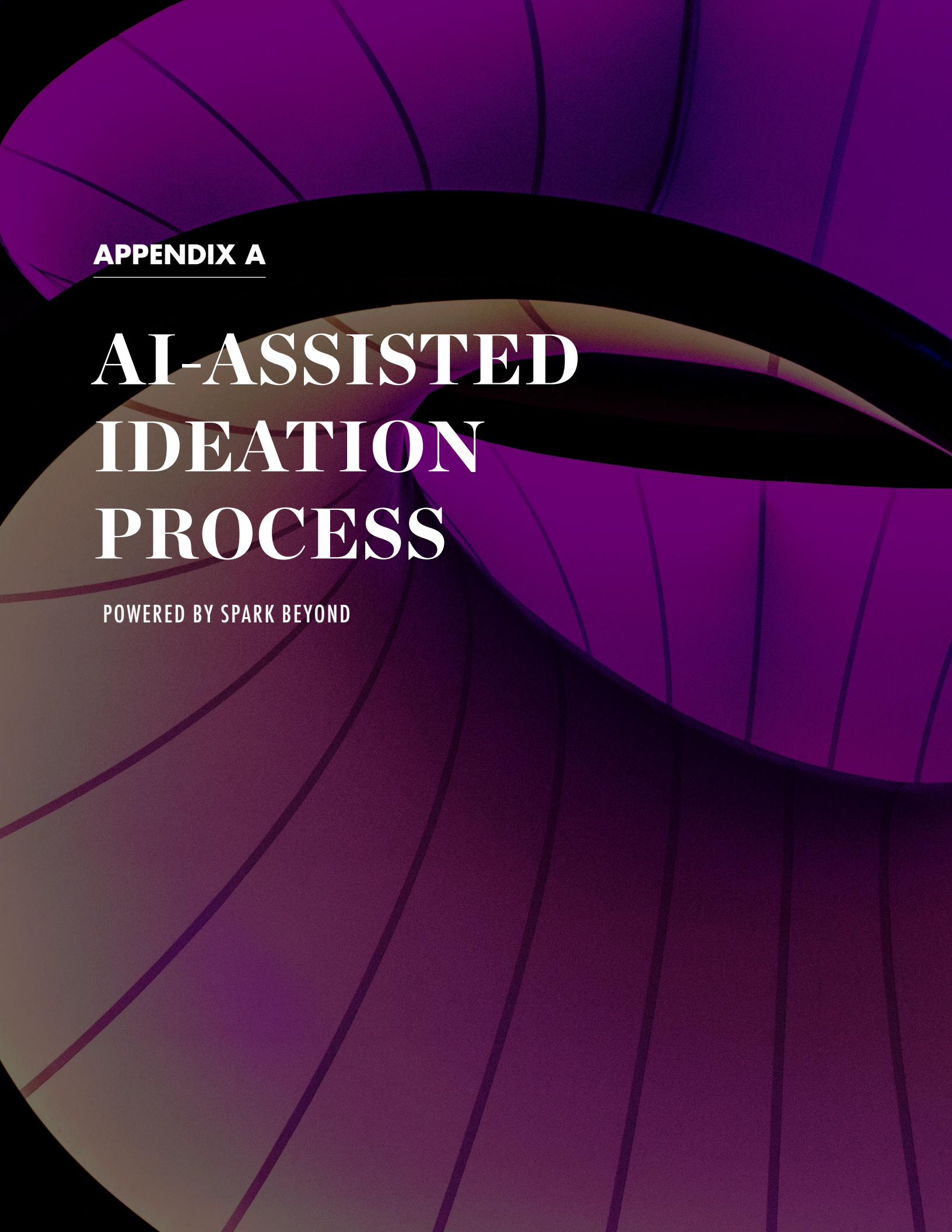
Available treatments in 2040 range from "simple" pills to genetic engineering of human cells, epigenetic reprogramming, and even some nano-robots that can conduct basic medical diagnostics and interventions in the body. No one treatment is enough to stop aging on its own, but their combined application in animal models demonstrates a powerful age-reversal effect.

Despite the results in lab animals, the authorities are still concerned about the side effects of such treatments in human beings. It is well understood that such powerful treatments may yet contain unanticipated long-term consequences, so their development and production are meticulously controlled. Genetic modification to remove predispositions to aging-related diseases looms on the public policy agenda. Perhaps the fiercest debates concern the genetic engineering of human embryos. Fears of weaponization of such technologies occasionally enter the conversation, as well. Not everything is completely figured out, and for some, uploading your consciousness to the cloud and even cryo-freezing the brain remain appealing supplementary options in hopes that these technologies will also see breakthroughs in the next generation.

Nevertheless, such potential drawbacks and risks are but a bump in the road to radical life extension. As science and technology advance, so too will the efficacy and safety of longevity treatments. For those who wish to live forever, the year 2040 is full of hope tinged with anxiety, as they know that by surviving just another decade or so they will have likely reached the promised land of radical life extension.

ASSESSMENT

In this transformative future, nearly all conditions have been fulfilled to enable the ideal longevity scenario. Early-stage life extension and age-reversal treatments have started making their way onto the market, and though they are just making their initial first steps, even more powerful solutions will soon follow. The main force that energized these breakthroughs was hope: hope that has caused governments to increase public spending; hope that has drawn thousands of young and bright researchers to the field of longevity; and hope that helped bring about—and was kindled and strengthened by—one successful breakthrough after another.



APPENDIX A

AI-ASSISTED IDEATION PROCESS

POWERED BY SPARK BEYOND


A

APPENDIX A:

Introduction

AS A SUPPLEMENT to our research process, we conducted an AI-assisted ideation session with 69 experts in the fields of longevity, life extension and futures studies. The goal was to develop novel ideas for the fight to stop aging. The process was designed in collaboration with AI firm Spark Beyond, whose algorithms first identified keywords and topics by scanning a draft of our report. From there the algorithms generated a set of provocative questions about potential ways to solve some of the Grand Challenges. The experts were presented with a random sample of these questions, sent directly to their smartphones and computers, and their answers were recorded and analyzed.

All together, 116 ideas were generated in less than 45 minutes. Since the number of ideas is so large, we will only review a few of them. As can be expected from any good One expert received a question from the AI engine about cell and tissue replacement: how would he suggest changing the process' order of operations? The expert came up with the idea of implanting a foreign organ in a patient's body in a way that would enable the patient's cells to infiltrate the new organ and gradually replace the foreign cells and tissue.

Such an idea has the potential to revolutionize tissue engineering, which is one of the most important remedies for aging.

POWERED BY

SPARKBEYOND

The Self-Replacing Replacement

ONE EXPERT RECEIVED a question from the AI engine about cell and tissue replacement: how would he suggest changing the process' order of operations? The expert came up with the idea of implanting a foreign organ in a patient's body in a way that would enable the patient's cells to infiltrate the new organ and gradually replace the foreign cells and tissue.

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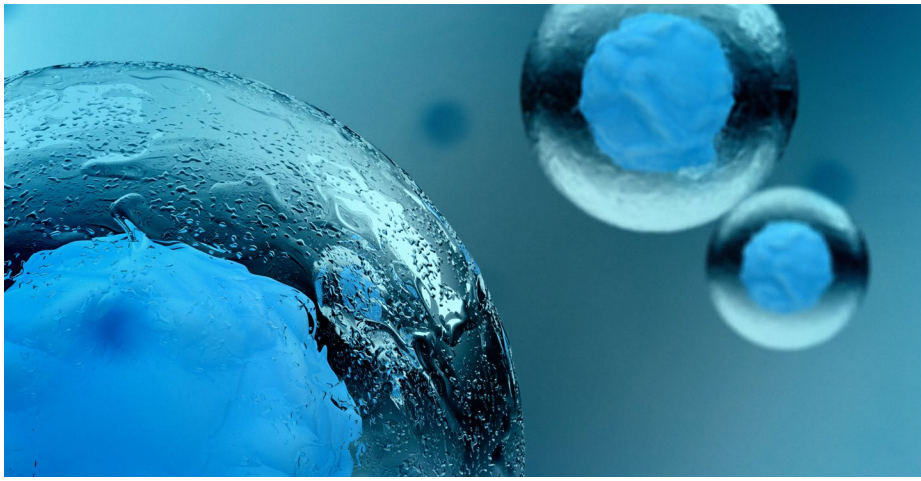


Blood-to-Blood Mapping

IT IS WELL known that blood transfusions and parabiosis can cause lethal immune reactions. In mice, parabiosis is often accompanied by the enigmatic "parabiotic disease", which kills nearly a third of the experimental mice within a week or two. It is suspected that the cause of parabiotic disease is an immune rejection response, but not much is known about this kind of response

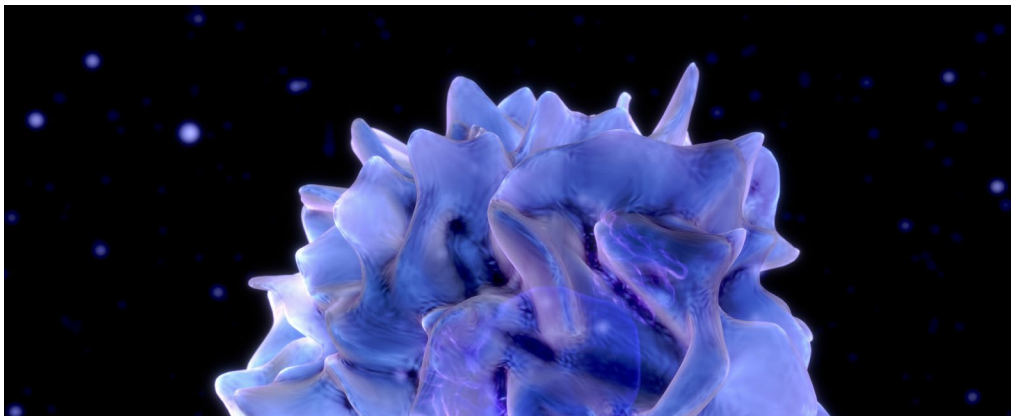
One of our experts was asked how the harmful aspects of blood transfusions could be used to obtain some positive effect. The proposed solution was that the immune reactions following blood transfusion should be recorded, mapped and analyzed per patient and per donor. This process could reveal more about the inner workings of parabiosis in mice and possibly in humans as well.

EXAMPLES OF AI-GENERATED IDEAS

Suicidal Senescent Cells

ONE EXPERT WAS asked how the order of operations underlying senolytic and senomorphic therapies could be changed in a useful way. As a reminder, senescent cells are believed to be one of the main catalysts of aging-related diseases and conditions, and these therapies are supposed to eliminate them or reduce their negative impact on the body.

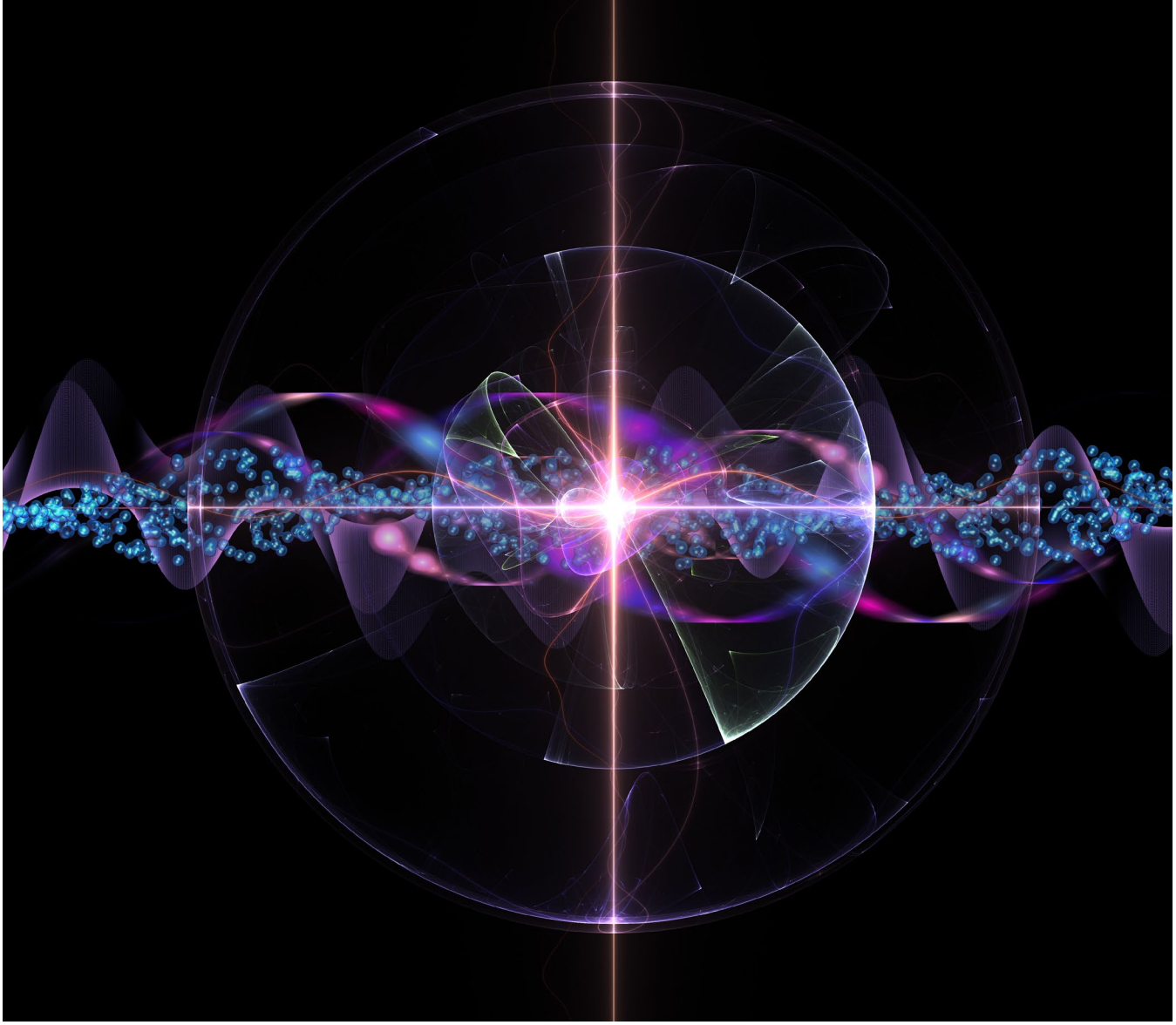
The expert suggested an idea to have the "toxic" effects of senescent cells redirected toward themselves and other senescent cells, so that they would eliminate each other. This idea could conceivably be adopted by senolytic and senomorphic therapy researchers. They could, for example, engineer senescent cells in a way that would make them more vulnerable to their own molecular signaling, or make them more attractive to white blood cells that would eliminate them from the body.



Disruptive Genetic Engineering

ANOTHER EXPERT WAS asked to come up with an invention based on the amplification of the harmful effects of genetic engineering to the extent that it would actually provide some benefit. The expert suggested magnifying the off-target and random effects of genetic engineering in tumor cells, in a way that would disrupt the cancer cells' ability to proliferate, migrate, or even sustain themselves in the body.

Given that cancer is one of the most lethal aging-related diseases, this idea could have a substantial impact on human longevity.



Conclusion

XPRIZE IS COMMITTED to encouraging people and organizations to bravely step out of their comfort zone, and we are grateful to Spark Beyond for supporting this goal with their machine learning tools. Examining old concepts in a fresh new light can drive tremendous progress, and using exponential tools to do so is fully in line with the mission of XPRIZE.

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