VADUZ ROUNDTABLE

INTERNATIONAL INSTITUTE OF LONGEVITY

Toward lifelong vitality

a coming revolution

Vaduz Roundtable | June 17-18, 2019

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> **Health is a state of dynamic equilibrium between the internal and the external environment.**
>
> Hippocrates (ca. 460–370 BC)

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FOREWORD

For more than two hundred years mankind has had an uninterrupted cycle of population increase accompanied by a rise in individual life expectancy. Science, new technologies and industrialization have led to greater food supply, better hygiene and a staggering improvement in medical services. This has led to less child mortality and increased life expectancy, both enhancing population growth. The proportion of the aging population in society is increasing. The trend is likely to continue.

Science In longevity has managed to explore and decode the process of aging, which is the main reason for chronic conditions such as cancer, diabetes, dementia, respiratory and cardiovascular diseases. The results are helping to rejuvenate and increase not only life expectancy but especially healthy life span.

This provides a happier life and helps overcome the perception that the active part of life ends at a certain age, in many cases in the 65th year. It also contributes to solving the grave problems of society to meet the cost of healthcare and pension payments in a rapidly aging society.

Interesting projects are being developed mainly in the U.S. and new businesses are being created. Business is the driver of innovation and needs investment. Good progress is being made. Europe is lagging behind and there is still much to do. Business start-ups need incentivizing through financing by investors. Insurers, regulators, governments and the medical profession should be alerted to the need for preventive health and healthy aging.

In their meetings, the Roundtable Foundation is addressing the most disruptive developments of our time and intends to find measures and solutions to turn difficult situations into opportunities. This is a paper containing the results of our first Longevity Vaduz Roundtable, which was conducted in collaboration with the International Institute of Longevity. We look forward to further meetings supporting ideas and solutions to promote preventive health and healthy longevity.

VADUZ ROUNDTABLE

Prince Michael of Liechtenstein

Founder and Chairman of Geopolitical Intelligence Services, Chairman of I&F Ets. in Vaduz, Board Member of the International Institute of Longevity.

INTERNATIONAL INSTITUTE OF LONGEVITY

Joanna Bensz

Founder & CEO of the International Institute of Longevity.

PREFACE

This document is the result of a two-day roundtable discussion in Vaduz, Liechtenstein by a group consisting of 20 international age science and longevity sector experts from North America, Europe and Asia.

The Vaduz Roundtable is an informal and interdisciplinary circle of experts brought together to exchange thoughts on crucial challenges in geopolitics, economics, finance and technologies. It is headed by HSH Prince Michael von Liechtenstein to address issues and to facilitate the implementation of ideas. The Longevity Vaduz Roundtable held in June 2019, was the first one organized jointly by the International Institute of Longevity with the Vaduz Roundtable Foundation facilitating the process.

The Longevity Vaduz Roundtable is one of the activities the International Institute of Longevity carries out to validate the common vision of the sector to support the promotion of the longevity sector in Europe.

This first roundtable brought together an extraordinary group of experts representing different interests and experience in the sector, which is designed to make a real difference to the focus and reputation of the longevity sector in Europe.

The main objective of the meeting, besides gathering a group of open-minded and professional experts, was to reach conclusions, make recommendations and document them in a white paper. This white paper will obviously be distributed first to all participants, followed by interested parties on academic, political, public administration and business levels. As the discussions were held under the Vaduz Roundtable Rule, the document does not attribute contributions nor identify participants.

Goals:

- to define a common understanding of longevity and healthy aging
- to produce a set of recommendations for the future of the sector
- to identify the major opportunities and challenges in the sector
- to identify ways of raising the profile of the sector in Europe and to incentivize major stakeholders e.g. business, science, governments and the medical profession
- to find ways of establishing best practices in the sector
- to establish ways in which various stakeholders can work more closely together

EXECUTIVE SUMMARY

We are at a historical inflection point from both a scientific and societal point of view. In the last few years, longevity biotechnology has changed dramatically and is becoming much more attractive to investors and scientists. The growth and most of the research is occurring in the U.S., followed by Asia and Europe.

Also dubbed the *silent revolution*, a new, worldwide wave of disruptive power is coming that will sweep away old patterns of life and transform our healthcare systems and modes of doing business. The medical industry has to evolve from being primarily a sick care system to concentrating on *preventive healthcare*. This requires effort and collaboration between research, business, regulators and other governmental authorities, education and especially the medical sector. The main goal is to achieve an increase in healthy life span. Science now substantially comprehends the mechanics of aging, which will enable the development of measures to avoid age-related diseases such as dementia, diabetes, cardiovascular diseases and cancer.

The longevity industry will permeate every walk of life, bringing an unprecedented opportunity to prolong life due to medical and technological advancements, as well as developing a new social contract for all.

Based on a two-day roundtable discussion among a number of world experts in the field, we have addressed the key issues for future changes in the coming years that impact three areas: aging research, the longevity economy and preventive healthcare.

1. Understanding the potential of the longevity sector and its significance in the future

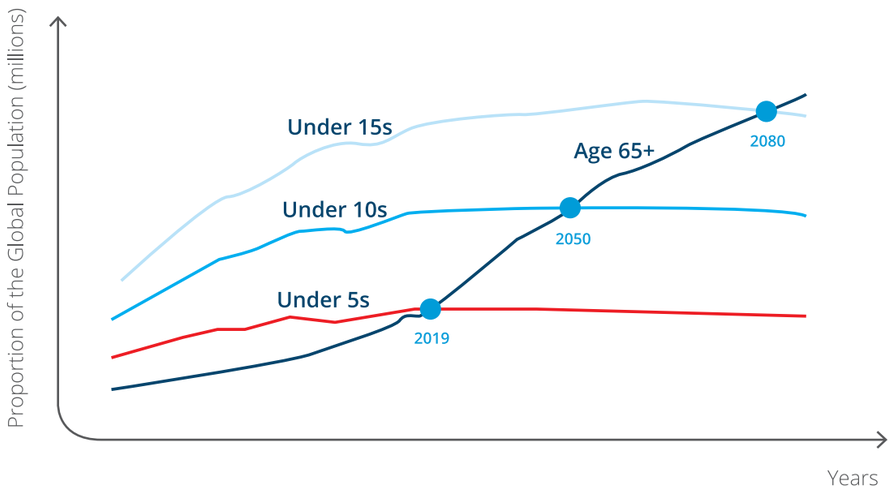
1.1 AN INFLECTION POINT FOR RESEARCH AND SOCIETY

One of the most visible transitions that we have observed in the last 100 years in demographics is the rapidly growing number of people aged 65+. It is estimated that in the next 40 years, this upward trend is going to continue and the number of older adults in society may reach up to 40 percent of the global population. This in turn is going to have enormous implications for the economy and healthcare systems.

In March 2019, for the first time in the history of humanity, the number of 65+ globally outnumbered children under the age of five.

This trend is likely to continue and will affect societies and their functioning.

Figure 1. Global Population 1970-2090



Source: United Nations

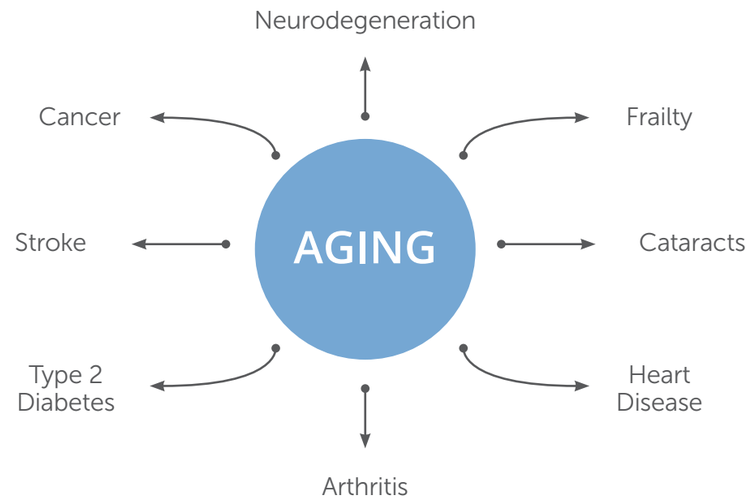
The increase in lifespan and the higher proportion of the population above the age of 65 is a result of the unprecedented developments that have taken place over the last 150 years, most prominently including the industrial revolution, advancements in medicine, improved sanitation and vaccination standards. Our life span has increased at the rate of about 2 years every decade. Based on that, it is possible to make a projection that the average life span will be 88 by 2050 and 98 by 2100. This will have a profound effect on our society.

1.2 THE CURRENT PERCEPTION OF AGING

The aging sector struggles with self-definition and public perception as it brings negative connotations of a perhaps long but also frail and disease-afflicted life in its last stage. There is a need to formulate a new set of perceptions around old age promoting vitality, well-being and wellness, both in research and policies, rather than a reliance on terms such as aging research, age-related disease management or handling inevitable frailty.

Entering the age of late maturity for most people unfortunately means being afflicted with one or more of the chronic diseases of aging including cardiovascular illnesses, cancer, Alzheimer's and Parkinson's disease, type 2 diabetes, glaucoma, macular degeneration, osteoarthritis, osteoporosis, hearing loss and sarcopenia (loss of muscle mass).

Figure 2. Aging is a Driver of Chronic Disease



Source: Buck Institute

„Biological aging is by far the major risk factor for virtually all of the major chronic diseases."

Source: Global Healthspan Policy Institute

A significantly greater number of people suffering from one or more of those conditions creates an epidemic, a real emergency that calls for immediate action. There is an 80 percent chance that a person in a developed country will have one of those conditions by the time they reach the age of 65. The implications are grave, both financially and socially, as people who are ill and disabled by age-related disease require prolonged and costly medical treatment, as well as a pension paid to them for longer periods than previous generations. Of equal import is the tragic loss of human potential and productivity, along with a poor quality of life and lack of social connection.

To complete this grim picture of the future of our society, it is important to mention the growing number of people that will be affected by dementia and other neurodegenerative diseases within the next 40 years. While the increase will be quite significant in high-income countries, another 100 million of them will be afflicted, not surprisingly, in low- and middle-income countries, which is more than alarming. These are the predictions made and confirmed by the National Institute on Aging, the National Institutes of Health, and the Department of Health and Human Services in the United States, as well as the World Health Organization.

While medical and technological advancements have helped greatly to extend lifespan, this is not the case to the same extent with healthspan. The two variables are not convergent, with healthspan being much shorter than expected. The statistics show that a person who lives to 80, on average experiences frailty and suffering for approximately 16 percent of their life.

That is why people, when asked if they would like to live longer, often say no, as their first image of a longer life is associated with pain, suffering and a lower quality of life. However, if the question is whether they want to live in good health and vitality beyond the threshold of 100 years, most would say yes.

> **In the majority of higly developed countries, 75% of all deaths are linked to 9 aging-related disease. Aging is the strongest risk factor for developing these diseases.**

Source: Global Healthspan Policy Institute

The task of changing the perception of the sector is initially challenging as the new paradigm touches almost every walk of life and policy, including healthcare systems, business opportunities, insurance plans, education, public financing, research realignment; and, even more problematically, it requires a radical change in mentality, starting from politicians and policy-makers through business management and more universally, the public.

1.3 THE NATURE OF AGING

Within the last 20 years of insightful and accelerated research on aging, scientists and doctors have been able to come to a greater understanding of what the mechanisms of aging are.

Lately, a number of European scientists have come up with a model confirming that there is no one single cause of aging. Aging, and the age-related diseases that come with it, are the result of multiple hallmarks of aging, which include [Dr. David Sinclair "Why we age and why we don't have to", p.17]:

- Genomic instability caused by DNA damage
- Attrition of the protective chromosomal endcaps, the telomeres
- Alterations to the epigenome that controls which genes are turned on and off
- Loss of healthy protein maintenance, known as proteostasis
- Deregulated nutrient sensing caused by metabolic changes
- Mitochondrial dysfunction
- Accumulation of senescent cells, which inflame healthy cells
- Exhaustion of stem cells
- Altered intercellular communication and the production of inflammatory molecule

Figure 3. The Hallmarks of Aging

Source: Carlos López-Otín, Maria A. Blasco, Linda Partridge, Manuel Serrano and Guido Kroemer, Cell. 2013

Human aging, as has been found, is about the loss of maintenance and a decreasing ability of repair and resilience in the body. Massive progress has been made to identify and activate repair systems' building resistance. Interestingly enough, the process of aging is not uniform and varies from one person to another, which in turn, has significant consequences, as will be explained later.

Figure 4. What is Aging? Loss of maintenance, repair and decreased resilience.

Source: The Buck Institute

There is an important scientific aspect to be taken into account, which says that the process of aging is actually malleable and varies from one human-being to another.

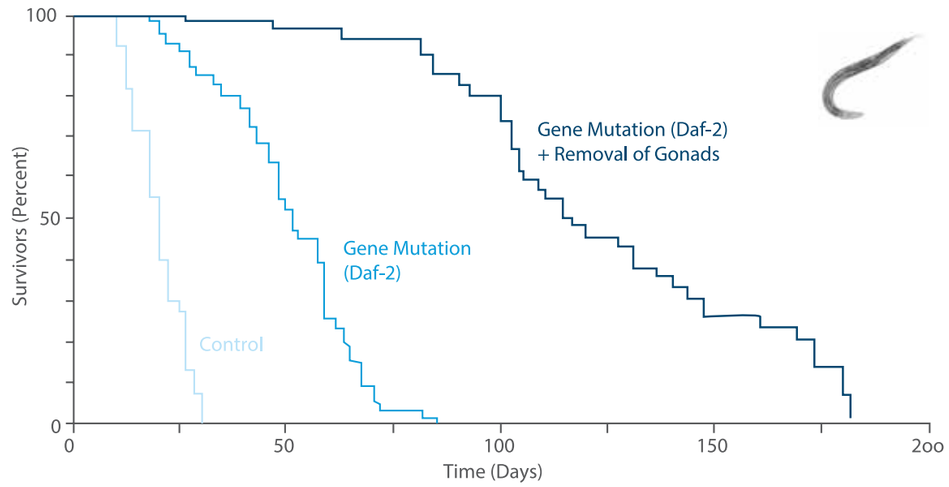
Scientists who conduct studies on the biology of aging, from which a new research discipline has evolved known as *biogerontology*, have discovered that it is worth concentrating on early, presymptomatic changes in the organism that herald aging and, what is more important, began to think about aging as a type of disease in its own right. Thus, the logical conclusion and hypothesis for aging can be constructed as follows: "if the aging syndrome could be treated as a disease, the associated diseases would be treated as the top of the cascade where they originate." [Jim Mellon &Al Chalabi citation from "Juvenescence – investing in the age of longevity", p. 28]

Experts are, however, divided on the question of whether aging should be defined as a separate disease. Doctors and physicians tend to claim that aging is simply a high risk factor, such as high cholesterol or genetic conditioning. For their part, researchers of longevity mechanisms advocate the categorization of aging as a *complex disease syndrome*.

The scientific evidence also suggests, which is a breakthrough finding, that aging is not as immutable as we once thought and that it is a malleable process, which although still not easy to interfere with, further research could help control.

While the calorie restriction method first used by Clive McCay has made it possible to prolong the life of mice in laboratories by between 25-65 percent depending on the calorie input, experiments in worms, conducted by Cynthia Kenyon, were a real breakthrough in the field. Daf-2 gene mutations resulted in prolonging the lives of worms by nearly 100 percent with even more spectacular outcomes after the removal of gonads. Most surprising is the fact that worms that lived three to eight times longer than the control group were also fit and agile in later life.

Figure 5. Genes Control Life Span



Source: The Buck Institute

Studies on animals are a good start and the potential is visibly enormous. Gene mutations are among the easiest ways to increase lifespan. These discoveries inspired many researchers worldwide to analyze lifespan mechanisms. It is worth mentioning that counterintuitively, changing life span sometimes may not require a conglomerate of genes as might be expected, but as in the case of C. elegans worms, just one, e.g. the rapamycin inhibiting mTOR pathway. That seems to universally extend life span in worms, fruit flies and mammals, so there is a high probability that it would apply to humans as well. Here, the task of biogerontology is to explore this phenomenon further, especially since the effect not only extends lifespan, but also healthspan.

The scientific evidence also suggests, which is a breakthrough finding, that aging is not as immutable as we once thought and that it is a malleable process, which although still not easy to interfere with, further research could help control.

Figure 6. Medicine in the 20th Century
Source: The Buck Institute

The goal of gerontologists and longevity experts is to increase the healthy years of life.

1.4 NEW APPROACH TO MEDICINE

Although advancements in medicine in developing treatments and drugs to cure chronic diseases have been spectacular over the last 100 years or so, with its siloed, fragmented character and focus on treating illnesses, medicine no longer addresses the issue of healthspan.

With every five years passing of life, the one's risk of developing one of the deadly quintet of ailments (cancer, heart and respiratory diseases, dementia, diabetes) rises exponentially, so the initial cause of all of these conditions is aging. Even if one of those conditions is cured in the patient, there is a high risk of developing another quite soon. If we find the cure for cancer, for example, the estimates indicate that life expectancy would rise by only two and a half years. Such a result does not address the issue of the one-directional and inevitable aging process. By the age of 80, we have a 30% chance of developing Alzheimer's. All of these diseases are caused by the same phenomenon, which is *aging*.

What we experience today is not a healthcare system, but rather sick care, organ treatment, and clear-cut boundaries between areas of medicine. The system is designed to react to the symptoms of disease - waiting for people to get sick, managing the diagnosed conditions and applying universal, one-size-fits-all drugs, irrespective of the patient's genetic background. A similar approach can be observed in the organization of big pharma companies.

New medicines aimed at aging should be system-based, i.e. driven by an understanding of the molecular mechanisms of aging, with geroscience being a way to address the issue in a holistic manner. It should be preventive and proactive and most importantly, personalized, using the genome of a patient, various self-diagnostic high-tech devices and other targeted interventions that are expected to be developed within the next 20 years.

Figure 7. Focusing on Aging to Change Medicine

Sick Care		Healthcare
Organ-based	→	System-based
Reactive	→	Proactive
Disease Management	→	Preventive
Universal	→	Personalized

Source: The Buck Institute

1.5 THE PERCEPTION OF THE CONCEPT OF LONGEVITY

For many, there is difficulty in grasping the difference between lifespan and healthspan. Contributing to the confusion are ideas and statements of possible immortality. This is perceived as a privilege of the rich. Furthermore, the claim of immortality might ruin the reputation of the sector.

One of the most important immediate challenges for the field is to better define the terms *lifespan, healthspan* and *longevity*. The public has to be informed that by addressing the morbidity of aging, the suffering of millions of people can be alleviated.

The goal of gerontologists and longevity experts is to increase the healthy years of life.

When looking at disease-free survival statistics, the natural group of people that are aging better than others are centenarians and supercentenarians. Interestingly enough, their healthspan is also significantly longer (by 6-16 percent) compared to other groups.

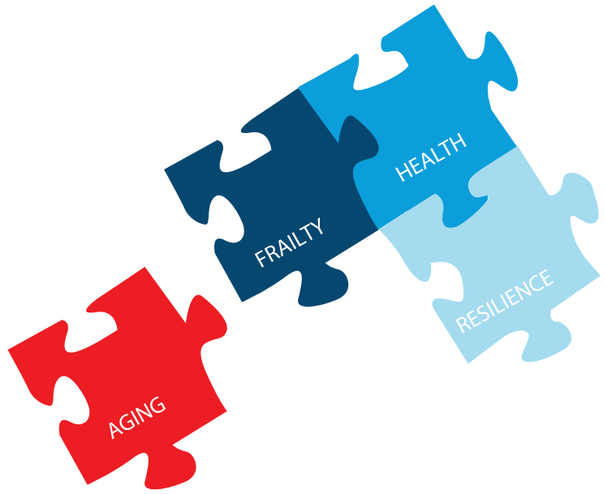
1.6 A CHANGE OF NARRATIVE

The siloed approach to medicine demonstrated by the organization of organ- or disease-based treatment translates into a correspondingly fragmented structure of research institutions, like the National Health Institutes in the U.S. and many others worldwide, which results in similar budget allocations and funds distribution. The spotlight on diseases takes place because they take a toll in death, but it does not address the issue of aging.

Aging remains a major risk factor for developing serious or chronic age-related conditions. When growing old, people lose their resilience and ability to perform, even the best of athletes in perfect health. According to the scientific community focusing on the biology of aging chronic diseases are a consequence of the process of aging.

The emphasis of medicine should shift from disease to health and from frailty toward resilience. It should be measured precisely when resilience starts to decrease in order to prevent premature frailty. Then the puzzle of longevity will be completed.

Figure 8. Resilience and Frailty



Source: NIA

Observing the rapidly increasing number of people 65+ in a growing number of countries all over the world, alongside the falling figure of births, aging is perceived as an urgent and large -scale problem. This causes an excessive burden on society and especially on the pension system. International Monetary Fund statistics show that within the next 10 years, with the exception of sub-Saharan states, all of the countries of the world, will experience a massive explosion in older citizens. A diminished workforce will no longer sustain the ratio of workers to pensioners necessary to secure funds for retirement benefits.

The topic of aging may become overwhelming if we continue addressing health the same way that we did in the 20th century. The attention so far has been on diseases and public health issues such as better sanitation, the development of vaccines, and more accessible health services. Such methods, however, are not going to address the chronic and more complex conditions of the 21st century.

People suffer from chronic diseases for two reasons: the biology of the disease in question and, more importantly, aging. Aging is the number one risk factor and universal, as it pertains to all chronic diseases. Since aging is a broader component contributing to developing a chronic malady,

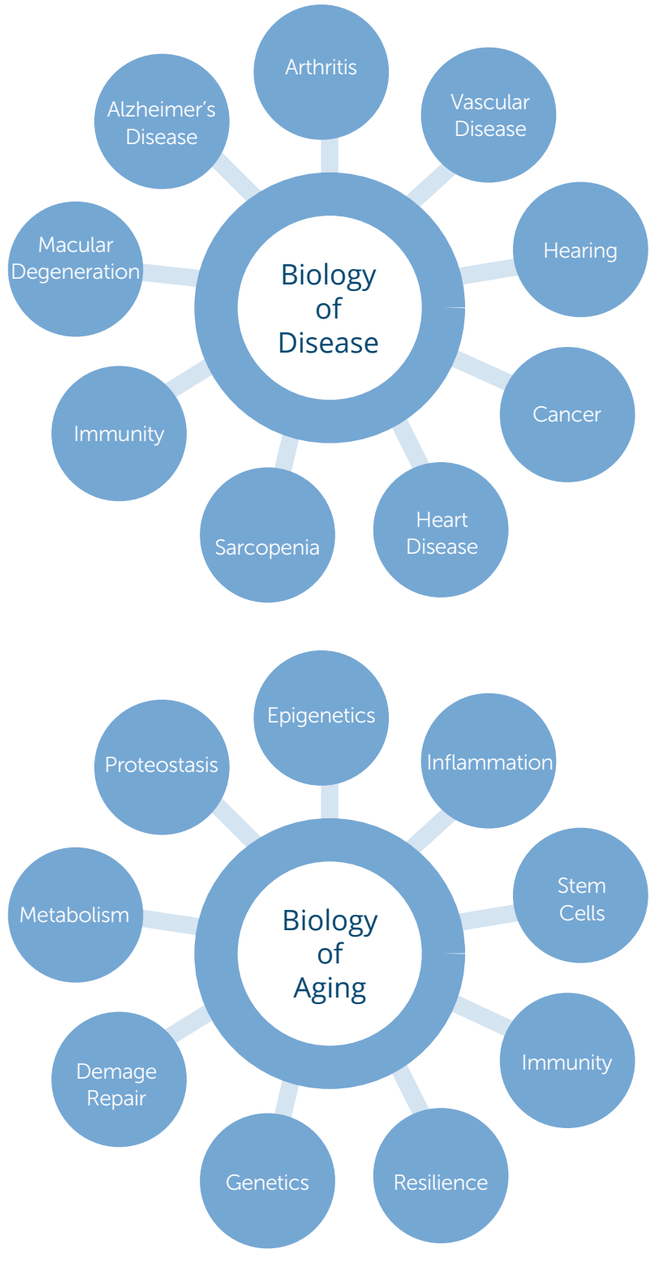
> **We believe that by addressing the biology of aging we will have an opportunity to find out not only what kind of disease a person is going to suffer from, but rather when he or she is going to get it.**

Genetics, lifestyle and environment are the major determinants of the type of ailments a person is likely to suffer from.

1.7 A GEROSCIENCE HYPOTHESIS

By analyzing the biology of aging, embracing studies of proteostasis, metabolism, epigenetics, inflammation, stem cells, genetics, damage repair and finally, immunity and resilience, we can prevent chronic diseases, rather than react to them when they occur, as with the current disease-oriented approach.

Figure 9. The Biology of Disease vs. The Biology of Aging



Source: NIA

The new discipline of science emerged to challenge aging as a separate concept, recognizing it as the primary cause of all the diseases. Geroscience can help reduce the rate of aging and thus, automatically, the rate of occurrence of all age-related diseases.

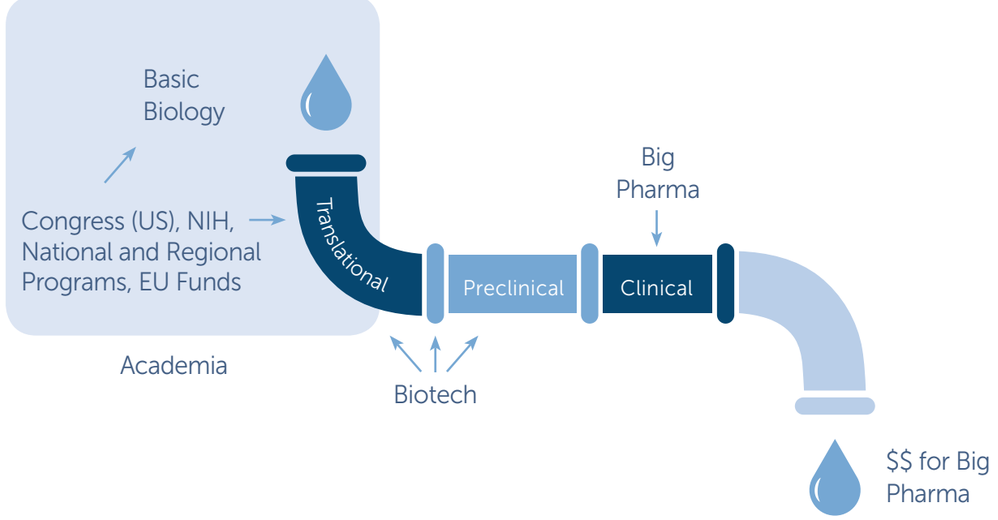
By targeting aging, a number of conditions and, more interestingly, health components such as frailty, fatigability, sleep disorders, urinary incontinence and chronic pain can be managed. This is often ignored by traditional medicine.

While sick care i.e. traditional medicine addresses conditions such as stroke, cancer, diabetes and neurodegeneration, all of them have a common driver. Aging remains at the root of chronic diseases, and to fight them, we should attack the primary cause.

1.8 FINANCING R&D IN LONGEVITY

At the moment, research on the biology of aging is primarily performed by academia and specialized institutes. This stage of studies, if we look at the U.S., is funded by the National Institutes of Health, supplied exclusively by public funding. Biotechnological start-ups and investors tend to pour money into both basic research and the translational stage, mostly as far as preclinical trials. However, the most fund-consuming clinical phase is financed by the pharmaceutical industry, an entity which benefits most from the results of the drug development pipeline.

Figure 10. The Healthy Industry Ecosystem – sources of funding



When we look at the funding structure in the U.S., we notice that the private sector invests five times more into health R&D than public institutions such as the National Institutes of Health, with $150 billion compared to the public sector's $30 billion, spent mostly on disease-focused studies.

The new discipline of science emerged to challenge aging as a separate concept, recognizing it as the primary cause of all the diseases. Geroscience can help reduce the rate of aging and thus, automatically, the rate of occurrence of all age-related diseases.

Hence, the new and challenging role for aging and disease-specific advocates, philanthropists and investors is to support research development and find ways of funding clinical trials.

At the beginning of 2019 the World Health Organization introduced an extension code to ICD for "age-related", that can be added to any existing disease code. This decision potentially brings the industry closer to classifying aging as a disease, which would give major financial incentives for drug companies to develop medicines capable of treating the mechanisms of aging directly.

A multistage life

The new health industry, with greater attention paid to aging, demands a different approach. It has to reach beyond the standard life stages from birth through childhood, training and producing to reaching the frailty phase at 65, followed by retirement and death. The different approach should incorporate extended periods of activity with retraining between the forties and sixties. Novel active life opportunities beyond this age can provide additional life purpose and as a result shorten the frailty phase. The goal is to secure a healthy period for as large a group of people as possible and give them an extended, quality life.

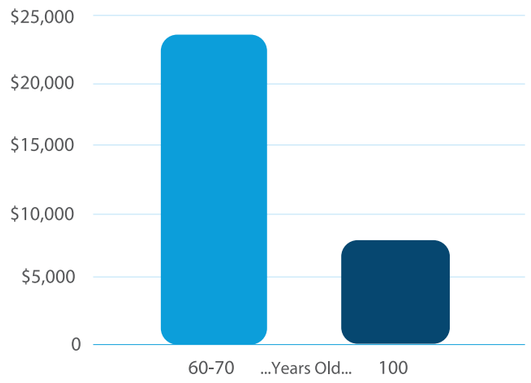
1.9 ECONOMIC IMPLICATIONS OF LONGEVITY

The implications of supporting the idea of people living longer with a greater quality of life, health and well-being has a multitude of consequences for society and the economy. When challenged by those who claim that more older adults and longer living people would increase the burden on society and budgets, we should analyze some numbers. The medical costs of the last years of life of centenarians constitutes only a fraction of the funds necessary to cover the treatment of 60-70-year-olds afflicted by the most common age-related chronic diseases of our times.

A longer and healthier life span has a vast range of consequences for the economy and society that will require changes in policies. The new generation of healthy older adults needs to be activated again and become productive in new ways adjusted to their needs. This phenomenon needs to gain acceptance in society as a life pattern that offers fresh opportunities.

According to the international investment community, the longevity economy has a potential value of $6 trillion and may become the most important industry in history in terms of scale and impact on the whole of humankind.

Figure 11. The Medical Costs of the Last Years of Life



Source: The Buck Institute

1.10 A FIXATION ON THE AGE OF 65 AS A CAESURA IN LIFE

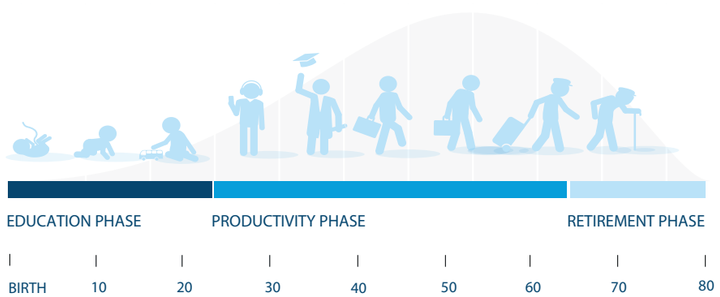
The fixed point between the active stage of life and retirement at the age of 65, adopted by numerous countries and governments, seems not to address the needs and dynamics of the current older generation.

We need to recognize that there are those who do not wish to continue working following the standard retirement age and those who cannot imagine their life without an occupation and activity.

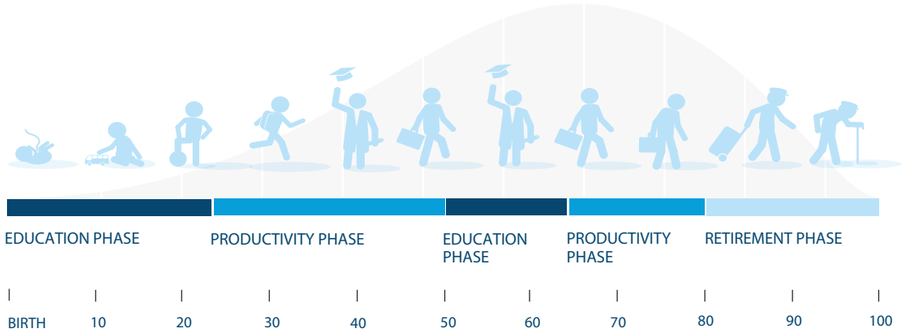
As a result, there is a need for flexibility and for the creation of a variety of opportunities for people 65+ who have a wide variety of backgrounds and experience and can make significant contributions.

Figure 12. The New Stages of Life

From the traditional 3-stage life....



...to multi-stage life



Source: Andrew Scott, Lynda Gratton "The 100-Year Life – Living and Working in an Age of Longevity"

1.11 THE IMPACT OF PUBLIC AND GOVERNMENT INVOLVEMENT

To make a real impact, breakthroughs in longevity should be accelerated and more importantly, made accessible to the public, reaching the market with concrete solutions. With approximately 30 compounds worldwide being developed in clinical trials at the moment, the pace of progress is extremely slow.

It is time for governments to understand that there is pressure on budgets caused by an aging population which demands support for solutions and setting of the necessary frameworks.

Currently, 95 percent of appropriated public funds goes into methods and devices to help older adults cope with the challenges of the aging process while only 5 percent is devoted to discovering the biological mechanisms of aging, of which far less than that is devoted to delaying aging. This is much too little to address aging as a separate phenomenon. The longevity area must not end up like gene therapy which, after 20 years, has been limited by a disease-oriented approach and confined to the scope of rare diseases. In this context it is important to note that in the longevity space, billions of dollars have been invested in addressing Alzheimer's disease and, so far, the failure rate for drug development is 99.6 percent (source: Chemistry World on July 14, 2014, www.chemistryworld.com).

The goal is to give an additional five to seven or more healthy years to people, and without a shift in treatment, we are not going to achieve it.

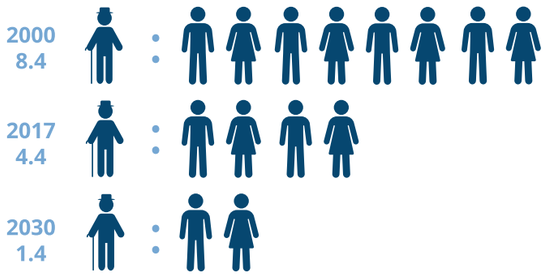
The complexity of the longevity sector and its need to define itself and attract attention and funds poses another important challenge: how to communicate with the public.
The message on progress in age science and benefits of longevity, their economic and social advantages is met with insufficient understanding in the public, the pharmaceutical industry, and even in the medical profession.

1.12 AN OVERVIEW OF LONGEVITY RESEARCH ADVANCEMENT WORLDWIDE

At the moment, research in the field is most advanced in the United States, equally in terms of the number of research centers, in scientific progress and the volume of investment. Europe is following suit and accelerating as well, with new policies in the United Kingdom and Scandinavia, valuable research in Switzerland, Spain and Germany and elsewhere.

The situation in Asia is harder to clarify with each of the leading countries developing separately. Japan is the most advanced in descriptive research on centenarians rather than biology and aging. China has numerous talented young researchers and is accelerating, but their expertise does not yet match that of American research progress. South Korea is also engaged in longevity research. The Singapore government takes a very practical approach which is expressed in policies. It is experiencing one of the fastest-rising aging rates in the world. The government estimates that by 2030, the workers' replacement ratio for every retired person will fall to as little as 2.1 in contrast with 8.4 in the year 2000. The authorities have identified the consequence of the problem i.e., an insufficient number of employees to pay for the care of the retired group, let alone a lowered quality of life. They are planning to address the problems of healthcare in the perspective of at least 10 years ahead.

Figure 13. Declining Old-Age Support Ratio



Source: NUS

The total life expectancy in Singapore is increasing much faster than the healthy life span. This is probably also the case in most other developed countries.

Life span extension agents

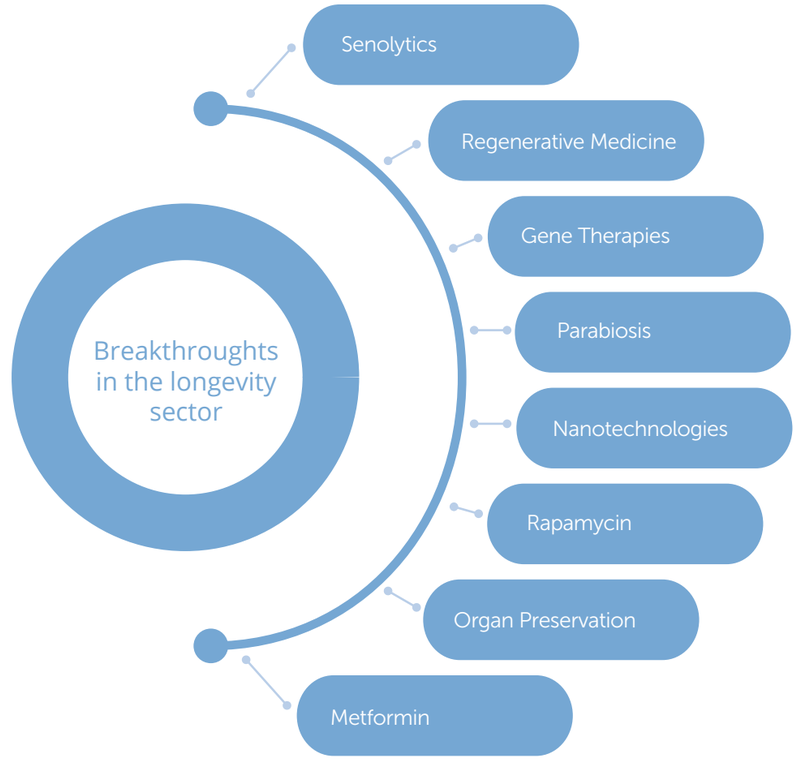
Figure 14. Healthy Life Expectancy – Sweden (2016)

	MALES	FEMALES
Life Expectancy	80.56	84.09
Healthy Life Expectancy	73.0	73.3

Source: Eurostat, Healthy life years statistics

Life span extension agents are twofold: behavioural, through calorie restriction, exercise and intermittent fasting, and chemical, with various molecules under study, such as rapamycin, metformin, NSAIDs (nonsteroidal anti-inflammatory drugs), NAD precursors and senolytics, to name a few. Recent tests of rapamycin and mTOR inhibitors on humans aged 65+ have proven to be very promising. They appear to extend health span and resilience against, for example, influenza quite effectively, and encourage further research. A molecule called AKG surprisingly mitigates frailty in mice by 50 percent, while extending life span only by 5-10 percent. This natural product compresses morbidity in mice and can potentially be translated to humans.

Figure 15. Breakthroughs In The Longevity Sector



Source: Global Health Policy Institute

Looking at the map of ongoing studies and testing, it can be ventured that it is much easier to slow aging and maintain health than it is to treat the complicated chronic ailments once they have already afflicted the organism.

It is much easier to slow aging and maintain health than it is to treat the complicated chronic ailments once they have already afflicted the organism.

1.13 INTERVENTION DESIGN AND A MAP OF BIOMARKERS

The Centre for Healthy Ageing in Singapore offers a unique, comprehensive approach toward aging in the framework of specific programs leading to the achievement of two main outcomes: aging prevention and aging management. They comprise analyzing mechanisms of aging, biomarker development, intervention development within the translational phase, clinical studies and, last but not least, demographic and economic studies. The biggest challenge that now remains is how to translate the results and preclinical interventions into humans, as their number is already significant and ready to be developed to the next stage.

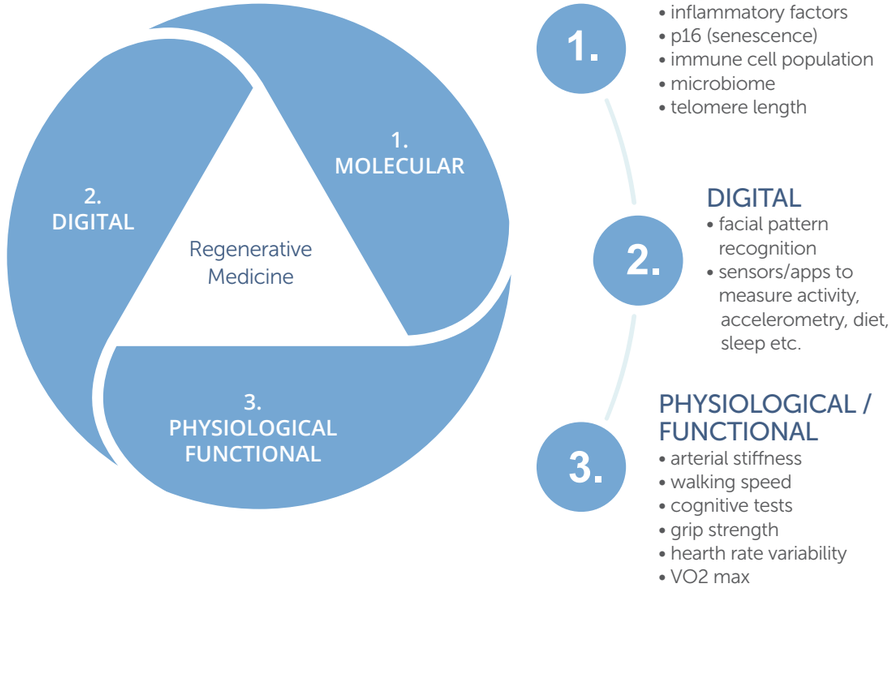
The existing studies on intervenional agents such as diets, supplements, stem cells, drugs or lifestyle patterns are scarce and incomparable as they yield different output. The idea is to build a platform of integrated biomarkers, test them and check which ones are most effective in healthy aging. This will be done in small test groups - with biomarkers as outputs for aging - representing a relatively healthy population with a view to designing a simplified model that would allow comparison of the effects of all known biomarkers.

In measuring aging progress, the most common biomarkers fall under the physiological or functional category based on results of arterial stiffness, walking speed, cognitive tests or heart rate variability. They are very effective with the 70+ cohort, while there is a need to detect aging symptoms much earlier and predict functional aging. Thus, to complete the picture, there is a need to include and test both molecular and digital biomarkers supported by artificial intelligence (AI) potential.

Much is expected from the molecular category, which encompasses the epigenetic clock, inflammatory factors, the NAD metabolome, microbiome and telomere length based on deep molecular data sets. We need to verify their response to various interventions, and what they measure when predicting morbidity and mortality. Digital measurements with facial patterns recognition, sensors or applications that monitor sleep, activity or diet, are also very promising as they offer continuous data accumulation and a personalized approach.

An interesting aspect worth mentioning is the low invasiveness of age measurement methods, which is crucial if we want to cover a large population. This can be offered, for example, by age-predicting 3D facial pattern recognition technology. However, it is not completely reliable yet, as many people look young and healthy, even if they suffer from serious diseases.

Figure 16. Biomarkers of Aging



Source: Centre for Healthy Ageing, NUS

The Centre for Healthy Ageing in Singapore is currently involved in studies of aging biomarkers of acarbose and rapamycin, AKG and other molecules using AI databases, with a particular age study of the Singapore multicultural and genetically diverse population composed of people of Malayan, Indian and Chinese ancestry.

2. Preventive healthcare and technology

2.1 STRATEGIES AND OPPORTUNITIES FOR PREVENTIVE HEALTHCARE

Sociodemographic changes and global nutrition trends affect the way people consume foods. Today, malnutrition has become a widespread problem beyond the traditional reasons, such as crises in food supply or as a consequence of sickness and very old age. Approximately 30 percent of the human population is considered overweight or obese. A person with excess weight can suffer from hidden malnutrition - living on empty calories - which can lead to an inadequate intake of micronutrients such as minerals and vitamins. This nutrition imbalance is linked to barriers in affordability of healthy food in many areas of the world and partially explains the huge gap in life expectancy and disease prevalence based on socioeconomic status.

This inequality of access to healthy nutrition is further aggravated by demographic aging. While access to affordable, healthy nutrition needs to be improved, public health can clearly benefit from greater engagement of the consumer in seeking healthy nutrition.

Today, people increasingly associate health with good nutrition and we expect this trend to grow.

Recent and important developments are the digitalization and personalization of nutrition adjusted to the needs of an individual. We know the basis of healthy nutrition at the population scale, but the response to various foods can be entirely different from person to person. Studies have shown that even genetically identical twins can have quite divergent responses to specific nutrition, which may be related to differences in the microbiome or environmental factors. Personalized approaches will provide a powerful tool to optimize the impact of nutrition on health and help people adhere to specific dietary regimes that may be necessary due to diseases.

General interest in maintaining health until old age is more and more popular, and much of this momentum is driven by insights from longevity research that has surfaced as a dietary trend in many countries. An example is the chronic or periodic restriction of total caloric intake, such as intermittent fasting, which has become very popular as a means to improve health. While the clinical evidence for the long-term benefits of intermittent fasting and caloric restriction is not fully established, a large body of evidence indicates that these strategies can lower the risk of cardiometabolic diseases, such as diabetes and stroke, as well as reduce the risk for certain types of cancer.

Figure 17. Trends Impact Food Demand

Source: Nestle Research

These developments are substantiated by longevity science, which explores the cellular processes that contribute to the decline of physiological function with age. This decline manifests in reduced cognitive function, such as memory loss, muscle weakness, and cardiovascular disease. The science that explains the molecular principles of aging has evolved rapidly in the past years from the free radical theory of aging, which postulated that the production of free radicals leads to damage to cells and tissues, toward a holistic understanding of cellular aging. Different molecular processes have been described that accumulate damage on proteins and DNA, where the genetic information is stored, and impair the regenerative capacities of tissues. For example, mitochondria, the cell's powerhouses, are critical to supply energy for all cellular functions and it is now well-established that the decline of mitochondrial function is a key driver in the aging process. Preclinical and early clinical evidence indicates that strategies such as intermittent fasting show promise in maintaining the cellular energy production capacity of mitochondria with age and thereby reduce the risk in a wide range of common chronic diseases. In addition, targeted nutrition approaches through natural bioactives that help maintain mitochondrial function, are emerging and could in the future, be applied to prevent the onset or progression of age-related conditions.

2.2 THE IMPACT OF HEALTHY NUTRITION

Nutrition has a major impact on well-being and the prevention of age-related diseases. On a population level, it has become clear that a balanced diet based on unprocessed foods that are low in simple sugars, rich in whole grains, fibers and certain lipids, such as omega-3-fatty acids, are key to maintaining health. A healthy lifestyle and balanced nutrition are the fundamental pillars to prevent cardiovascular disease and to lower the risk of the most common chronic diseases. In addition to healthy nutrition, preclinical studies in a wide range of laboratory models have consistently shown that dietary strategies like caloric restriction, as well as the supplementation of food-derived bioactives, have a potentially positive effect on extending healthy life span. These natural bioactives, such as NAD+ precursors or specific polyphenols, show promise as targeted nutrition for preventive healthcare.

Healthy nutrition, as well as targeted nutrition strategies in conjunction with exercise, are tools to empower individuals to take care of their healthy years or decades before age-related diseases occur. This approach is in contrast to today's healthcare models that are largely based on pharmaceutical interventions that are prescribed once the first illness symptoms appear, such as high blood sugar, osteoarthritis-related pain, or cancer. While at these stages, the chances of cure are often limited, the early stages of diseases are not well addressed today beyond the general recommendations of primary prevention, such as exercise and a healthy lifestyle. We foresee that progress in aging science, together with digital tools for personalization of nutrition, will pave the way for targeted and proactive healthcare.

This is where targeted nutrition comes in with its selected natural ingredients that improve mitochondrial health and delay aging. They act at the cellular level to, for example, repair DNA and support energy production, recycle and rejuvenate damaged mitochondria, detoxify free radicals and restore the consumption of fat. The compounds are based on robust research and a preclinical background and thus can be expected to perform well when translated into the human clinical phase.

2.3 THE ROLE OF MITOCHONDRIA IN PROLONGING LIFE SPAN

We are dealing with two genomes, one in the nucleus and another in the mitochondria, which has serious consequences. Mitochondria are responsible for producing energy, while the nucleus makes the body's building blocks. They need to communicate well, but as we age, this communication deteriorates. One of the ways to prolong life is to find modes of invigorating mitochondria and making them healthy and working efficiently for a longer time.

The first method is caloric restriction, which has been proven efficacious in a number of animal studies to extend life span. It increases the number of mitochondria and can be treated as a universal principle.

Secondly, boosting mitochondrial activity and their number improves lifespan, as well as leading to improvements in cognitive performance, as was proven in mice studies.

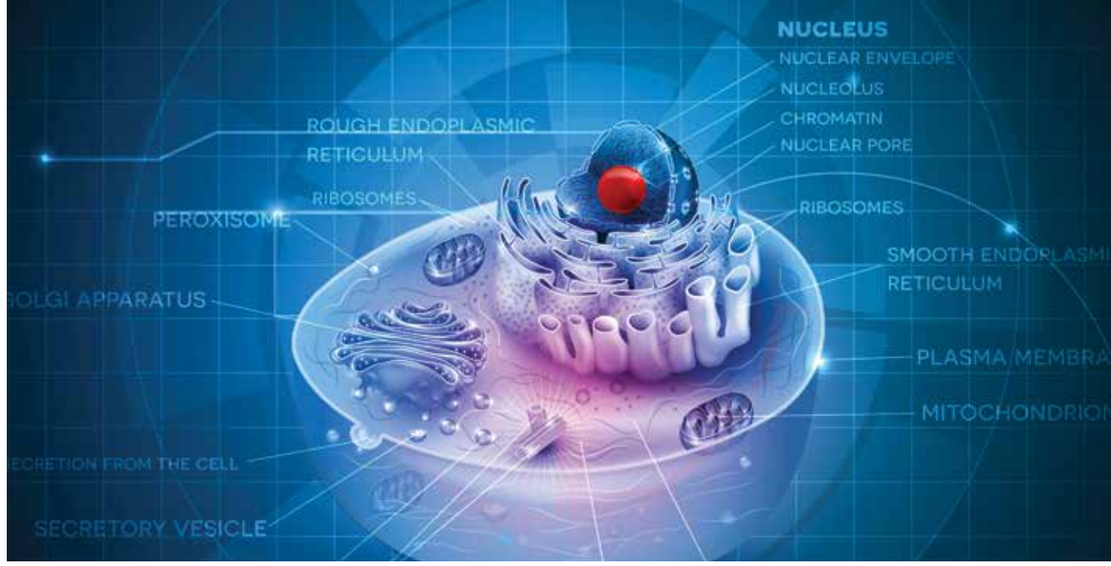
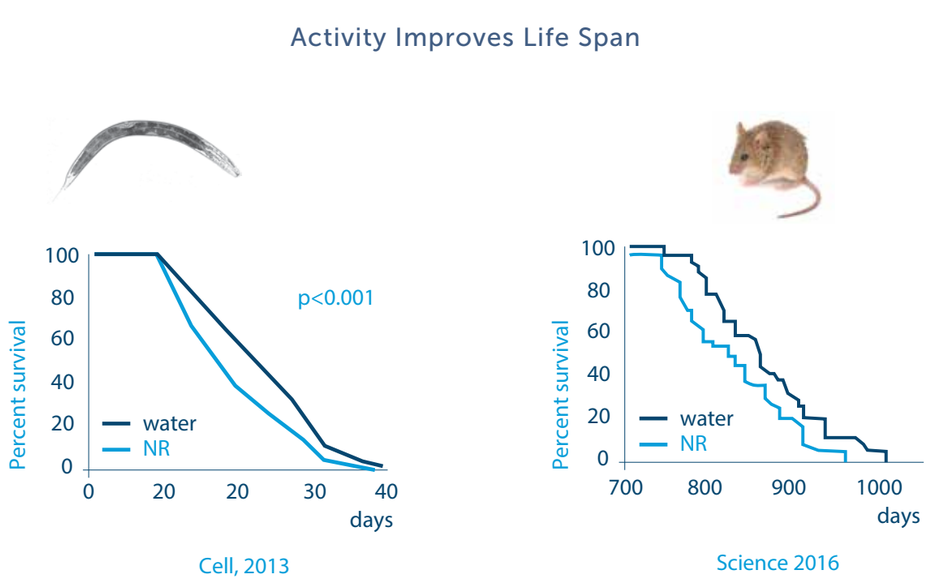


Figure 18. Boosting Mitochondrial

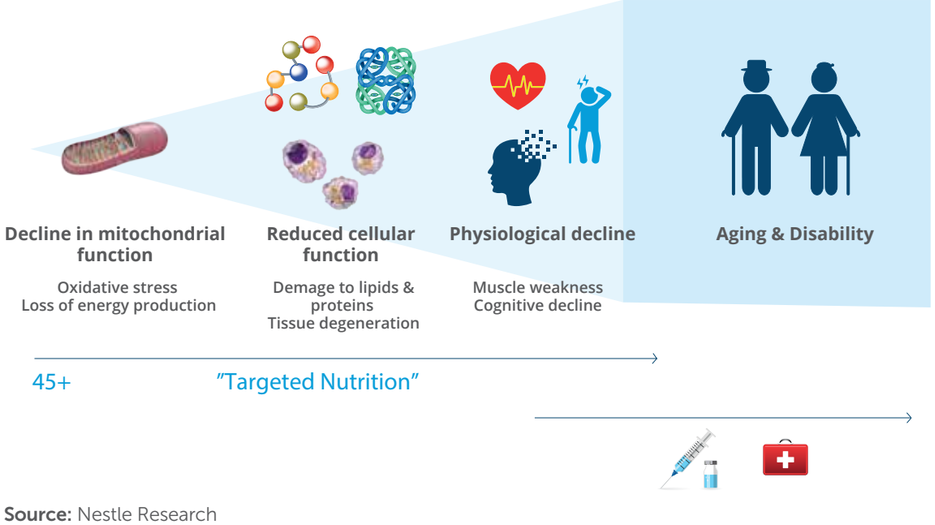


Source: EPFL Lausanne

What is new in mitochondria studies is the discovery that a reasonable amount of stress makes them work better. This could be a selected drug, bacteria, exercise, or any other intervention, which when applied in moderate doses, is beneficial to mitochondria and can increase life span.

Another way of improving the functioning of mitochondria is stimulating the recycling process called mitophagy, as seen, for example, with the active ingredient from the pomegranate. Mitophagy eliminates old mitochondria and strengthens healthy ones.

Figure 19. Mitochondria Drive Aging

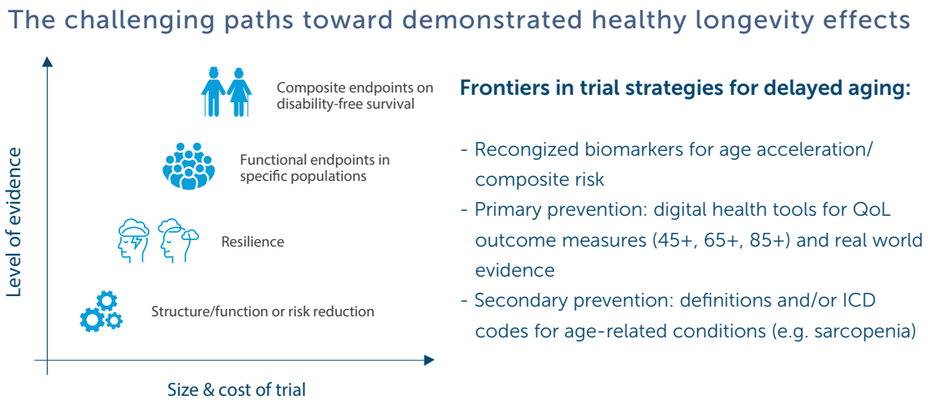


Source: Nestle Research

2.4 FOOD AS MEDICINE

The key challenge is presenting the evidence of *food as medicine*. The traditional manner of gathering convincing data is through preclinical stages one and two, based on biomarkers through large scale and very costly clinical trials on humans affordable only to big pharmaceutical companies. There are also intermediate trials in the form of resilience trials after bedrest and after surgery, immunosenescence trials, and response to flu vaccines. The higher the level of evidence required, the larger the size and cost of trials with composite endpoints on disability-free survival. This track is definitely too long and the entrance barrier too high to introduce food as medicine into clinical trials, so there is a need to find a smarter way to place them into the testing path.

Figure 20. Food as Medicine



Source: Nestle Research

The key challenge is presenting the evidence of food as medicine.

The frontiers in trial strategies for delaying aging encompass building a set of recognized biomarkers of age acceleration and adjusting digital health tools for quality of life measures for different generations and their needs (45+, 65+, 85+) under primary prevention. The problem with secondary prevention lies in defining age-related conditions under international classification of diseases (ICD) codes as the process is very slow. Previously, the treatment was elusive and general, i.e. do more exercise and eat healthy. When provided with definitions and criteria, it becomes easier to address it, in order to derive claims in clinical trials for new alternative treatments (which was the case of sarcopenia a few years back).

It is possible to put natural products, when well-tested and proven, into a prescription drug that has a reduced price and is easily accessible due to a reimbursement scheme covered by the patient's insurance company. In consequence, the company strengthens its credibility of research while the customer can make use of a natural and effective product at affordable cost.

Another issue is an overwhelming abundance of supplements available for any almost condition. Most of them are not confirmed or properly tested. To enter the market with a new scientifically validated compound or natural product is more costly and complicated, and often highly regulated.

2.5 SCIENTIFIC VALIDATION OF RESEARCH

For the longevity sector, it is now very important to conduct studies and do everything possible to translate the results that enable medical foods or specific drugs to be used by humans. While there is resistance, the credibility that stems from sound clinical studies is a protective shield against any backlash that might possibly occur and damage the field's image.

The products supporting healthy longevity would require validation at the level required for drugs, and as the process consumes huge amounts of funding, it is almost impossible to raise such money. So there is a need to find a middle ground where it is possible to generate credible scientific evidence in the context of aging and at the same time, work on natural products in partnership with food companies to make the trial costs reasonable.

At the moment, the longevity field is associated with hypotheses yet to be tested in human studies. Preventive medicine and food will need another few years to be fully developed and tested. The cost of the end product will not compensate for the cost of trials required to enter the market. Furthermore, these products have to have measurable effects to attract investors, and need to be included in the prescription regime to be reimbursed later. Then the cost for the consumer will be covered. Only through providing convincing evidence, securing the cost reimbursement mechanism and achieving an accessible price, will the sector be able to advance.

Experiences with rare diseases or drugs for children show that changing the legal framework was decisive in attracting interest and investment. The clinical trials under this new framework were shorter and patent protection wider and faster to obtain, and therefore developing such drugs for niche indications became viable.

In aging science, the reality is that we should not expect "a silver bullet," one molecule that will cure all diseases. One of the expected solutions can be a mix between medical foods and supplements as drugs. In some countries, there are already functioning schemes of reimbursement of medical foods. The problem is that some natural compounds will not bring the same response in every patient. Hence, there is a need to stratify people, to adjust the intervention to their specific needs.

2.6 BRINGING TOGETHER ALL ACTORS: REGULATORS, RESEARCHERS AND INSURANCE SECTOR

The question is how to create a "win-win-win" model that provides a patient with an effective, well-proven natural solution that has been approved along medical and legal standards, and enables insurance companies to reimburse costs, thus making it more accessible. As a result, the total societal cost should be reduced. Healthy, longer living patients do not require costly treatments that would become a burden on health systems and insurers in the long term.

To involve the latter, the products offered need to be well tested and deliver real effects, as insurance companies prepare their own simulations and estimations to decide on reimbursement.

At the moment, the regulatory path for a product to be brought to the market is very complicated and also places limitations on insurance companies and government agencies to cover the costs. To address that issue and secure safety and credibility, as well as increase its accessibility, a common effort of regulators, governments and industry actors has to take place.

2.7 MAJOR FIELD DEVELOPMENT BARRIERS AND POSSIBLE SOLUTIONS

The key obstacle is the way a natural product or a supplement can be labelled and made available. Drugs today enjoy the "treat/cure/prevent/mitigate disease" sticker, which makes them easy to recognize and be recommended by physicians and, ultimately, reimbursed by insurers.

Another barrier discouraging investors from funding comes from companies selling unproven compounds launched onto the market without sufficient monitoring. They can win at the expense of well-tested, regulation-compliant products because customers choose them based on their lower prices.

2.8 BIOHACKING COMMUNITY AND THE SOCIAL CLINICAL TRIALS

Apart from a growing number of highly aware customers who, for example, follow intermittent fasting and are interested in healthy longevity, there is a vast community of people willing to test various compounds or peptides on themselves to quickly ascertain the effects. Those

Recalling the doctor's maxim of primum non nocere (first, do no harm) and bearing in mind that all compounds and drugs may have side effects, it is vital to conduct sound clinical trials.

so-called *biohackers*, already accumulate data prior to the release of data from government commissioned studies.

The biohacking community, which now comprises hundreds of thousands of social media participants and millions of those interested in prolonging life with experimental substances, has become a new cultural phenomenon that could potentially be leveraged as a source of medical data. They could be involved in something that we would call social clinical trials, an alternative and cheaper way of verifying the effects of novel compounds.

It is imperative to keep in mind, however, that it is enough for one or two deaths to be reported for a whole field to be shut down or severely hampered for years ahead. This was the case in gene therapy that was hit by news of fatalities in 1995. Therefore, recalling the doctor's maxim of primum non nocere (first, do no harm) and bearing in mind that all compounds and drugs may have side effects, it is vital to conduct sound clinical trials.

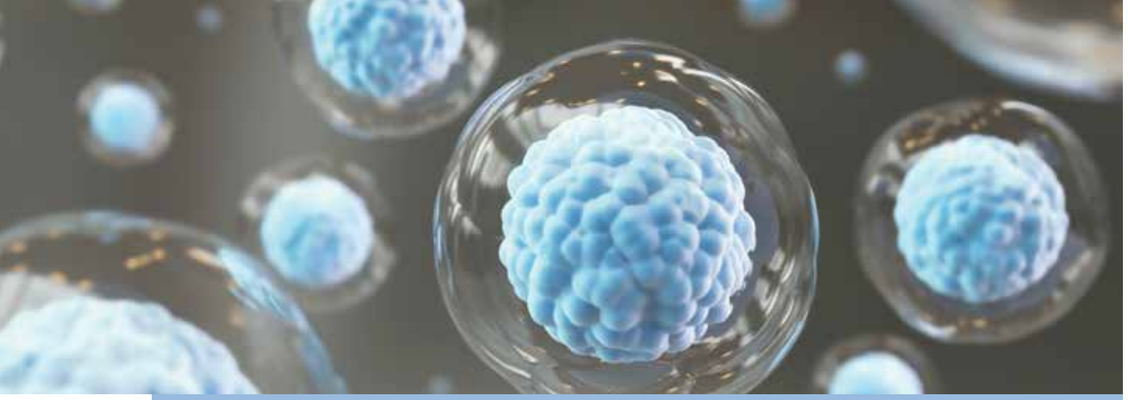
Public opinion is very sensitive to negative reports, as bad news is disseminated faster and is not easily compensated for by an overall positive performance within a field.

One suggested solution is to publish standard protocols for carrying out interventions with natural products or supplements and thus helping people to use them in the least harmful way. This should also be available as an online platform and web service for data gathering on the effects of products. With time, and more data, the standards could be improved and made more universal, while the best laboratories with the most credible results, could be certified and recommended. The tests should be low cost or ideally, free of charge.

When to standardize is also a difficult question. Standardization may increase safety and ultimately can provide benefits in the approval process, but can also stifle innovation, which is a concern in a relatively new field that is yet to find its path toward widespread human adoption. The challenge is to add credulity to clinical studies while enabling strategic development in human study design.

2.9 INCENTIVIZING A HEALTHY LIFESTYLE

It seems advisable that new insurance schemes should give people incentives to stay healthy on a daily basis, with some digital devices, trackers, and other wearables that would allow individuals to monitor and moderate their potentially risky behaviors. This, in a way, is currently happening with car insurance and can be translated into health and life assurance. In the U.S., for example, many employers and insurers have developed schemes that include major discounts for employees who do not smoke, exercise regularly, and/or the use health trackers. It is legal and is becoming increasingly popular.



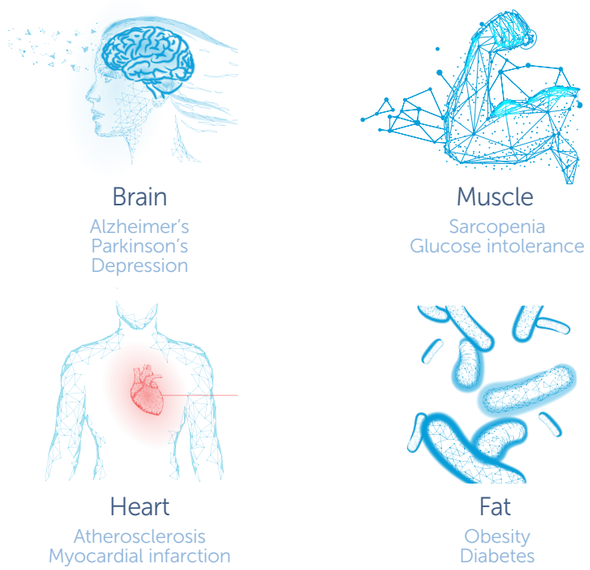
3. The importance of public debate, education and social campaigns

3.1 HOW TO BREAK THE PRO-AGING TRANCE

Throughout life, human genes operate in a way to boost activity, metabolism or procreation. And for a long period, the organism tolerates this amount of gene activity, until it gets to a threshold beyond which it turns out to be harmful,as a result of accumulated damage, and in late-life, leads to mental and physical frailty and ultimately, death. Among various health extension alternatives, a maintenance and damage repair approach is the way to stop the damage from becoming pathogenic.

Aging and age-related diseases should be viewed in a new way, distinguishing between diseases and health problems of late life that may also include conditions such as Alzheimer's or cancer on one side, and less-defined frailty, sarcopenia or immunosenescence on the other.

Figure 21. Aging, a Physiological Decline



Source: EPFL Lausanne

One of the goals is to convince people that the field is focused on health and vitality rather than aging. Aging is now associated with an increasing population of 65+, unequal access to treatment, as well as a collapse of the pension system.

To get more funding for research, gerontologists and other scientists involved in studying aging, should indicate (albeit stressing the speculative nature of such estimates) how soon a breakthrough may happen in extending life span and its quality of life. This was the case in the U.S. in the 1970s with cancer, when public announcements made by leading scientists led politicians to give them financial support in the national budget for many years ahead.

3.2 EDUCATIONAL PROGRAMS THAT CAN BE INTRODUCED IMMEDIATELY

Research has proven that metabolic life with its serious consequences starts in an embryo right after fertilization. The major factor is genetic material inherited from both parents, but especially from mothers. Their material is responsible for mitochondria, the powerhouses in the cells. Parents' dietary patterns can influence the life quality and child's inclination to chronic diseases before and during pregnancy.

With this in mind, policymakers could introduce a major improvement at a low cost and in a relatively short time by educating people about the impact of diet on the unborn child during pregnancy. This can be done by means of Massive Open Online Courses (MOOCs) that can promote healthy lifestyle practices and be made available to a large population and spread the message rapidly. This could prevent age-related diseases and contribute to healthy life span at the early stages.

4. The longevity dividend

4.1 THE INVESTORS' PERSPECTIVE

With the explosion of new technologies and the continuous refinement of medical therapies, the longevity industry has achieved momentum in certain regions within the last five years.

No doubt the revolution is coming and the question is not if but when it will happen.

With research on aging centers dispersed worldwide, located mostly in the U.S. and a few in Europe, it is difficult to talk about the sector's maturity. What it has to build within the next years is a reputation of a promising and reliable industry. To do so, the area would greatly benefit from an undisputed success, a therapeutic or an immunogenetic therapy to pass the tipping point and attract the interest of major investors.

Without such a breakthrough, many investors are unwilling to finance the longevity business. It simply poses too high a risk. They also demand relatively quick results and are not convinced that extending life span has positive consequences. In their view, investing in older generations leaves no space for the younger population to thrive.

To raise interest in the longevity industry, the message about the strengths and opportunities it offers has to be spread. There is a strong need for a professional communication strategy to reach out to potential investors and stakeholders.

Simultaneously, the field of aging needs to be wary, especially with the use of new pharmaceuticals and therapies, of harming and causing deaths among patients or customers. That balance between striving for innovation and progress, and safety combined with accessibility, has to be kept in mind at all times, avoiding a utopian perspective which could jeopardize the reputation of a reliable business alternative.

There are a number of misconceptions surrounding the idea of a larger cohort of older adults living longer and healthier.

Longevity experts underline the importance of older adult empowerment, to create opportunities for them to contribute actively to society, either by working longer and in flexible forms or participating in all manner of associations, NGOs, etc. or caring for other society members.

The latest studies of the economy show that a rapidly aging society is our current reality, including countries not only as obvious as Japan, Germany and China. The average human life span in Western and affluent countries is well above 80 for men and 85 for women. With the trend set to continue in the next 20 years, the mechanism of generational replacement on which the current pension system is based faces collapse. It is not going to handle the growing cohort of older people that will soon outnumber the young due to the statistically confirmed steady drop in the number of births in developed and emerging countries. The situation is exacerbated by the quite universal reluctance of politicians and governments to tackle the problem by increasing the retirement age.

What can be stated with a certain degree of confidence is that aging is changing. In the cohorts of 65+, one can observe those who are affected with age-related chronic diseases, as well as an increasing group of 80+ and older, with more centenarians than ever before, living in good health for longer, though often in isolation and loneliness.

As both groups constitute an increasingly larger proportion of society, their impact on state budgets is detrimental, in covering the rocketing costs of medical treatment and care, and in providing pension coverage for people who have their productive years well behind them, and may spend nearly as much time in retirement as they did in work life. So far, little has been done to respond to tackle this urgent problem as the system is based on arbitrarily adopted and chronological age-related life stages: birth, training, working time, and retirement.

A new approach presents an important observation, that people age at different paces and that chronologically age driven life stages do not address the problem, nor are they the most financially efficient. There is a burning necessity to restructure life stages, thus bringing in more flexibility and budgetary savings.

This is where longevity science comes in as it brings a better understanding of the mechanisms of aging across human lifespan, and has various tools to precisely measure *biological age* instead of chronological age, as is the current practice. This in turn could support policymakers in adopting a new approach toward old age, as only extending the retirement age does not solve the problem.

New aging paradigms and alarming demographic studies prove that we are facing a *longevity ®evolution* that will reshape not only work and retirement models, but also adult education and training. Decision makers have to face this new reality as quickly as possible and treat it more as an opportunity than a problem.

Longer life should keep people healthy and full of vitality as long as possible, while giving them a new *purpose for life*. The mission is to implement measures that support them in remaining healthy and happy.

The interface between financial, social and humanitarian aspects.

One of the ways of coping with the changing patterns of aging is to propose flexible working and retirement models, part-time vs. full time, early leave or prolonged working years, if health permits, with part-time employment, community service, and caring for children, to name a few. As a result, a new social system should be designed for longevity to be widely incorporated into the social structure and supported as the one trying to reduce the arduousness of old age for humanitarian, economic and social purposes.

Longer life should keep people healthy and full of vitality as long as possible, while giving them a new purpose for life.

Numerous stakeholders need to take on this responsibility and cooperate with others to create the right balance between regulation, innovation, finance, progress, safety and the reputation of the sector. Healthy and sustainable longevity requires a holistic approach that cuts across generations and upends the current life patterns. A *widespread collaboration* is necessary comprising governments, business, academia and the medical world.

Vibrant and healthy longevity should be included in regional, national and European strategic documents, budgetary plans and educational programs, to cultivate a healthy lifestyle and the disease prevention. This should encompass child, teenager and adult education. The rationale behind this is that we cannot stop aging, but we can slow it down with natural and affordable methods along with epigenetics, and improve its quality with the support of the latest technology, medicines and pharmaceuticals. The goal is to increase the accessibility of healthy lifestyle habits and supporting technologies, and to prevent discrimination or inequality. This will happen sooner when the longevity sector, both the research and business areas, are able to attract public and private funding to take advantage of economies of scale.

To start with, we need to define what each stakeholder or social or business actor can do to promote the idea of *lifelong vitality*. The question is who should moderate that debate and provide guidelines for Europe, as well as how the money inflow into the sector should be coordinated and incentivized.

The more reliable data on the positive effects of longevity for the economy and society is available, the more positive response we can expect from business and the public.

4.2 PSYCHOLOGY'S ROLE IN MANAGING HEALTHY AGING

Meaningful, sustained engagement is one of the variables that clearly discriminates between those who succeed in retirement from those who fail or perish. Social engagement correlates very strongly with biological condition and quality of life.

The name of the aging field and its definition is crucial and necessary to address first. If the cosmetic industry can sell vanity (looking good), no doubt geroscience can sell the concept of vitality (feeling good) or some other positively valanced equivalent.

It is strongly advocated to explore the understanding of the culture we live in and identify cultural clashes that occur in multicultural environments and societies. While plurality is a great value, a huge challenge is faced in creating a unified message on aging. Equally important are the framework and the division of responsibilities for marketing, lobbying and debate among the key actors.

4.3 THE ROLE OF THE EUROPEAN COMMISSION IN HEALTH PREVENTION

Since member states are in charge of their health systems and allocate funds to protect the health of their citizens, the European Commission can only complement the member states' actions. Thus, the Commission undertakes initiatives that individual states would not be able to conduct on their own and consider it more effective to transfer this capacity to a higher level, thus achieving economies of scale.

The lead project called "The Active and Healthy Aging Initiative" is a program that has been in place for the last five years and is designed to foster research and exchange best practices to promote active and healthy aging. It is a bottom-up initiative that not only supports older adults, but also focuses on how to more effectively cope with the problems encountered during aging. Run by DG Connect, it offers a wide range of online applications, wearables, gadgets, and software programs with the use of AI. All member states, their institutions and NGOs are strongly encouraged to participate.

There is an ongoing debate about designing new business models for drugs or treatments for rare diseases that are not economically viable but still crucial to the general public. Longevity science and its economy require a new approach, including in business models. It is advisable for their representatives to enter into the debate to find the best solutions to advance longevity in Europe.

The promotion of health is a priority for the European Commission today and there is a lot that can be done in health systems around disease prevention. However, educating a wider population has to consider that the absorption capacity for health-related messages is limited. Currently, it is mainly disease-related. The pervasive method of labeling all individual diseases is an obstacle to communication. There should be a joint understanding and definition of healthy aging and that would get the message across more effectively. The sector of healthy aging should be clearly positioned. There is a need to overcome the siloed thinking in communications about health.

The facilitation of the adoption of drugs or treatments that have been tested elsewhere is a very promising tool in the framework of the EU. There is an open system for each of the member states to submit best practices assessed under the commonly agreed criteria. It is quite clear that longevity would be eligible under this system. A best practice, compliant with the criteria, can be actively proposed by the European Commission to all other member states. There is a possibility for a country interested in setting up a project to facilitate knowledge transfer. This formula works very well and should be further developed.

Another trend in the EU is to encourage health promotion, shifting the emphasis from diseases to prevention. Currently, a group of 10 member states is interested in implementing a practice from Sweden that allows a GP to prescribe not only drugs but also physical activity. An OECD study demonstrates that this works, and people are more active when guided by their general practitioners.

The mortality-only cost of providing life insurance to a person leading an unhealthy lifestyle can be 10-15 times that of a person leading a healthy lifestyle.

It is worth bearing in mind that within the current political context, resources will be limited, and funds cannot be allocated to all goals.

A key problem these days is health inequality. Even if a new health intervention appears that, in principle, could improve all people's lives, there is a great risk that only part of the population would benefit from it and that it is not universally available or affordable.

4.4 HEALTHCARE COSTS AND INSURANCE ISSUES

Longevity is recognized by the insurance sector as a real challenge due to insufficient funding and poor estimates of life expectancy.

Poor estimates do not allow the calculation of randomness, which is the basis of risk assessment for the insurance industry.

Age science provides better tracking of probability in aging that would enable insurers to lower the cost for the consumer.

That, in turn, would change the role of insurers from companies from whom people buy a policy and are not in touch with until something goes wrong, to companies that help prevent things from happening and help people manage their conditions. That is a new direction insurers could play by means of a joint social-private effort as health insurance enablers.

It is worth mentioning that the data from wearable technologies and IOT could enable insurers, to cost-effectively facilitate prevention. The mortality-only cost of providing life insurance to a person leading an unhealthy lifestyle can be 10-15 times that of a person leading a healthy lifestyle. This could be utilized in other types of health insurance. If money can be credibly directed toward helping individuals lead healthier lives, the individual wins with no extra cost to the system. This was not previously possible due to the high costs of prevention, but technology is driving the cost of prevention lower.

Some insurance companies are already providing people financial incentives to live a healthier life. This should also, be supported by governments when setting necessary frameworks.
The new longevity challenge calls for close cooperation among governments, insurers, employers and individuals. We need a sustainable system of insurance that people trust, and to have a discussion to decide on how to provide funds for its implementation. Otherwise, there are going to be more frustrations and challenges in the near future. The debate should go hand in hand with the financial education of younger generations and adults.

To sum up, insurers of tomorrow will provide health monitoring services with bad luck protection, but the scope of bad luck will narrow as precision medicine emerges. Responsibility and information will shift to individuals from institutions. As this happens, a new social contract will be needed. It is essential for regulatory environments and benefit structures to align with the changes that are driving longevity, as well as with the consequences of longevity itself.

4.5 INNOVATION IN THE LONGEVITY SECTOR BY BUSINESS

To understand what is ahead of us as the rejuvenation revolution explodes, we need to imagine the potential benefits for individuals and society.

Under the rule of this silent revolution, there is a real chance that we will see the first generation of people to have aging under full medical control. We could immediately improve our health, directly reverse chronic diseases and be as healthy at 70 as at 30.

The world is now undergoing a transition from a state of being helpless about age-related disease into one in which we have aging and chronic disease under surveillance. It is still in progress, but the theoretical groundwork is in place and its evolution is accelerating. Drugs and therapies are already under development and treatments are already available like senolytics.

To speed up the process in Europe, the Forever Healthy Foundation, for example, is undertaking a number of initiatives, such as holding an annual Undoing Aging Conference centered on rejuvenation therapies for human application, which is held in Berlin (www.undoing-aging.org). The attendees comprise an interesting mix of scientists, start-ups, investors and media, including active bloggers on rejuvenation.

The second initiative is companies supporting rejuvenation start-ups that translate research into products that humans can use. This provides mentoring and financing to the start-ups that explore, for example, tissue regeneration, senolytics, TGF11 and macular degeneration.

The third component of the Foundation's activity aims to seize opportunities with the first generation of rejuvenation therapies, however simple and crude they may be at this stage. Rejuvenation Now encompasses: geroprotectors, existing compounds that slow the aging process or reduce the probability of getting an age-related disease, compensatory treatments that restore the level of hormones back to more balanced levels, and molecular and cellular repair with new senolytics, which are now being tested in human clinical trials.

It is also important to set up new standards of how protocols and guidelines are documented. Current available materials are often of low quality and not scientific in nature. There is a need to improve them by standardizing protocols for the use of antiaging compounds.

The introduction of significant capital would provide the sector with stability and enable it to anticipate what businesses and models it should be building for the future.

4.6 AGING AND AGEISM - THE WORLD HEALTH ORGANIZATION'S FOCUS

In the framework of WHO aging is not a prominent area and still underfunded. While it is gaining recognition and interest, this is still a slow process. Within the division of Healthier Population it falls under the Health Promotion Department together with governance frameworks, healthy settings, health literacy, physical activity and tobacco control.

Today over 1 billion people in the world are 60+. yet the highest spending worldwide still goes toward programs for children and teenagers and not towards work into curing age-related diseases. Globally, government expenditure on health increased as country income grew, except in low-income countries. High-income countries increased spending on health, even after the economic crisis of 2008-2009. Average expenditure in middle-income countries have doubled since 2000 due to economic growth, whereas low-income countries are still lagging behind. There is a trend, especially among upper-middle and lower-middle-income countries, to concentrate on domestic funding of health rather than relying on external sources of funds.

In its normative and technical capacity the WHO has come up with risk reduction of cognitive decline and dementia guidelines that provide information about what policymakers, healthcare providers and patients should do to reduce dementia risk. The emphasis is on preventive measures with a view to reduce dementia cases by 20-30 percent. Another initiative offers solutions on how to introduce Integrated Care for Older People (ICOPE) that is now being implemented in several countries.

Another key program embraces 900 cities in 41 countries covering 230 million people worldwide in the form of the WHO Global Network for Age-friendly Cities and Communities.

One of the major challenges, however, is a global campaign to combat ageism, in any form of discrimination that older people face every day, even in the most progressive countries. This is done in the form of reports, books, articles published and studies conducted to change how we think, feel and act toward age and aging.

Many surveys conducted on older adults regarding what brings them happiness show that the answer is clear: health and sufficient money to survive and buy affordable commodities, a meaningful role within society that enables interactions with others, and a healthy environment (clean air and water, quiet surroundings, housing). How to make older people happy appears to be simple and is also of interest to the WHO.

4.7 FINANCING THE HEALTHY LONGEVITY SECTOR

One of the ways to reach out to politicians and government officials who make decisions and allocate funds is to use a best-practices portal in health capacity created under the auspices of the European Commission.

When a pilot project has been completed and the evidence is available, it can be submitted to the portal following assessment by a panel of independent experts. Together with compliance with the selected criteria, the project should ideally demonstrate its economic viability and transferability to other recipients. Once accepted, the project would be demonstrated in special two-day fairs for government health representatives, among other best practices. Later, the level of interest would be measured among the participants and for most popular practices, we would set up projects that help implement those solutions in terms of knowledge transfer and actions that can work better jointly than individually. This mechanism is open to anyone that intends to share a particular health-related practice and should be very interesting for the longevity sector to showcase its achievements and spread the word about new approaches to a healthy life and longer life span.

We observe that there are clearly more practices available than the absorption capacity. There is no guarantee that a potential longevity pilot project will ultimately be implemented. However, it is still much better than the traditional approach that involves collecting various practices in an immense data collection while there is no evidence of interest in them. Practices that involve supplements or products for which anyone has a monopoly will not be accepted under the scheme.

The EC is launching a new Joint Action on implementing best practices in nutrition. Of member states 26 out of 28 have already applied to participate. It is worth monitoring its advancement.

Another way of acquiring funds is to gather major insurance companies to jointly invest in prevention schemes. This could be a common worldwide major effort to start a program with funds of around 100 billion dollars focused on major initiatives such as promotion of healthy lifespan, prevention trials for cancer, monitoring for diseases in younger generations and aging trials. The promise of huge savings on disease treatment should attract such companies, unlike big pharma, which is focused on curing diseases and unwilling to invest in prevention.

The availability of money is not the most acute issue; the problem is deciding on what kind of initiatives the funds should be spent. In the EU, there is a new budget for the years 2021-2028 being negotiated. Large sums at the level of approximately 10 billion euros have been earmarked for health so far and a similar amount could be allocated in the next budget. To select the priorities and spend the money in a smart and effective way is a real challenge. Very often, politicians prefer to choose projects like building hospitals to leave a tangible heritage.

To get to the point when the longevity field is ready to select practices for a pilot project, there is still the need to accumulate more data on how certain compounds, drugs or interventions work for human health and lifespan. Currently, there are a lot of hints and promising signals, but there is insufficient data. This is a transitional moment as the field needs a success story with clinical evidence for benefitting humans to boost and gather momentum. We are hopeful that generating sufficient and convincing data is likely going to occur in the next ten years.

5. Recommendations for stakeholders

The experts gathered at the roundtable came up with a number of recommendations and proposals on how to increase healthy longevity and on how to support the growth of this field in Europe. Stakeholders may take these into consideration when planning their strategies and budgets in the years to come for implementation of ideas and initiatives connected with the longevity industry.

Each of the recommended solutions should be perceived and implemented in the cultural context of local circumstances, be it European, country- or community-based.

For each of the stakeholders or sector aspects, the priorities are as follows:

GENERAL RECOMMENDATIONS

The longevity field is coming to a turning point and there is a window of opportunity to set up its foundation and sustain its development. There is a great need for a solid, well-rooted collaboration within the field to build the message as well as to develop tools to help it thrive and advance.
The longevity area is now transitioning from rebellious adolescence to adulthood. To implement real change, there is no need to fight the system, but rather to embrace all the existing structures including the medical community, the Food and Drug Administration (FDA), EMA and the biopharmaceutical industry. It is still necessary to stay progressive, have an agenda and drive changes, but it is impossible to have an impact from the outside.

To be able to introduce the longevity concept into the mainstream, it is essential to cooperate with physicians, raise their awareness and knowledge on aging mechanisms and novel treatments. This will inevitably involve all related business sectors.

Europe has a rich tradition of a healthy lifestyle with diet, herbs, folklore in different regions and countries, as well as a sound and well-established scientific infrastructure on which it can build its longevity story.

The so called big health project enforced in China making each citizen go to the doctor for a checkup in regular cycles is probably not the best example for Europe. However, the idea of continuous prevention should be at the core of our interest.

There is no doubt that without getting the medical profession on board, the longevity project cannot succeed.

We need to help to change our preconceptions and include the 65+ generation into the fabric of society. If we can connect traditional lifestyle with novel health promoting habits and drugs or supplements, the chances of success for the entire field will rise.

Europe has accumulated an enormous amount of practical and scientific knowledge on how to live long and healthy, but it is not currently able to translate it into action. Therefore, the need for a public debate and multilateral cooperation is urgent.

SECTOR BRANDING

- To formulate a new set of perceptions around old age promoting vitality, well-being and wellness, both in research and policies rather than research on aging, age-related disease management or handling frailty.
- To have a common understanding of what the sector understands under longevity, healthspan, healthy longevity and vitality.

EDUCATION AND PUBLIC ENGAGEMENT

- To place the educational and awareness-building emphasis on young people (as has been the case in Austria).
- To spread the message to the general public that aging is malleable (as currently, only around 1 percent of the population is aware of this).
- To educate teenagers and the general population that with a healthy diet, mobility and lifestyle, youthful energy and vitality can be retained.
- To develop a strategic plan incorporating pediatricians, health advisors, local authorities, business and pilot projects in healthy lifestyle choices and habits.

RESEARCH AND SCIENCE IN EUROPE

- To define a joint project for aging, ideally under the auspices of the European Union in collaboration with research institutes and interested companies.
- To develop a joint international project focusing on aging biomarkers and conduct further research to give the field momentum and visibility.
- To provide guidance on how funding for research on aging can be accessed, for example, from the newly-drafted EU program called Horizon Europe for 2021-2027.
- To encourage the ringfencing of resources for aging and longevity initiatives.
- To define differing goals, needs, treatment strategies and research required within the age groups 45+, 65+ and 85+.
- To stratify and establish a person's biological vs. chronological age using biomarkers to indicate the symptoms of aging, and adjust treatment or lifestyle recommendations accordingly.

FOR BUSINESS

- To incentivize business, the pharma and biotech industries, and the investment community to participate in longevity research and initiatives.
- To share knowledge about the huge economic potential of this field.
- To communicate the message that aging is one of the main risk factors for chronic diseases.
- To develop a network of researchers, investors, business angels and banks to facilitate contact and cooperation in concrete initiatives.

FOR INSURERS

- To prepare a value of life research paper to analyze longer life spans, their impact on the quality of life, and benefits to society and the economy. It should be written in accessible language, published and distributed among various stakeholders and the general public. This would demonstrate a proactive approach to the current issues of demographics, changing lifestyles and life duration.

- To devise a mutual insurance pilot project (with compensation in the event of failure) for a disadvantaged group such as families where a member suffers from Alzheimer's disease. Within this, to promote preventive measures such as diet, stress management and sleep, combined with additional coaching and treatment.
- To leverage successful outcomes of the above-proposed project to attract more funding from the pharmaceutical and insurance industries.
- To encourage insurance companies to play a role in subsidizing health management at an individual level. The tools are available today, but need to be more effectively communicated. For example, exercise, lifestyle and diet should be promoted under a primary prevention label, while with new or known products, such as metformin, recommendations and information should be given to patients for safe current use. People should also be apprised of their status regarding the advancement of clinical trials.

FOR EUROPE

- To conduct extensive research, if possible with the use of the OECD and its database, to identify the benefits of an extended lifespan such as the financial consequences of postponed retirement age.
- To rethink the idea of life stages, now quite arbitrarily divided into childhood, training, work and retirement, with fixed time spans, and to adopt a more flexible approach with age malleability in mind (chronological vs. biological age).
- To take a proactive approach toward the issue of the increasing population of 65+ and decreasing children cohort by embarking on longevity as an opportunity rather than a problem, introducing new schemes and policies that would address the changing needs of society
- To take advantage of Europe's strengths with diet patterns, lifestyles and food quality to build upon, accumulating best practices to share with other states and communities, and take advantage of regional initiatives.
- To create a European Roundtable for Aging, to which major players including governments, regulators and big pharmaceutical companies would commit. The goals would be to complete the most promising research on aging by funding costly clinical trials and to continue studies under a commonly agreed framework.
- To make Europe an important player in the aging field in terms of economy, health and well-being, it is necessary to identify all positive aspects and strengths that the continent already demonstrates, such as the Mediterranean diet, the popularity of cycling, a strong academic network, and medical research infrastructure. This could be communicated to stakeholders via a white paper. If the momentum is overlooked, the American companies and industry will take over the lead in aging and the ideas will have to be imported from overseas.
- To manage the complexity of the field by selecting priorities formulated in the framework of a strategic document that will attract interest and funding.
- To promote a healthy lifespan among the general public (planting the idea in the public consciousness analagously, as NASA is doing by advertising and educating about its mission). The idea is to communicate that aging can no longer be perceived as a problem and that we already have a solution.
- To fund a flagship research project in Europe that brings measurable effects and thereby draws the interest of various stakeholders and gains greater visibility for the whole field.

FOR EU INSTITUTIONS AND GOVERNMENTS

- To resolve the structural problem that the longevity community does not form a coherent group and cannot be identified as a player yet.
- To look ahead, to investigate what kind of aging and longevity projects have been conducted and financed in the framework of the Horizon 2020 EU program for science and innovations. When proposing new projects to EU programs, aging research can be referenced.

- To map what has been done so far to help build a structure of what needs to be studied further and what kind of projects and initiatives should be proposed.
- To educate the general public to understand that aging is modifiable and more and more of the current research confirms that. There are factors that help slow down aging. They are not controversial and would be backed by most researchers and could be promoted quite universally: diet, exercise, stress management and regular sleep.
- To place emphasis on areas where Europe already has gained some advantage. The approval journey of new medicines in Europe is less demanding than in the U.S. where requirements include high safety and efficacy standards. Approval should be sought at an earlier stage of medicine testing, with more thorough and sophisticated post-approval monitoring, which could be described as adaptive licensing.
- To leverage Europeans' modern understanding of aging where researchers writing about it gain relatively high visibility, which can be translated into political action and the development of priorities based upon it.
- To use the absence of research districting between aging and age-related diseases to encourage increased research funding. This novel approach should not raise controversy among the public or jeopardize the position of politicians.
- For the EU to create a framework and funding mechanism for research projects in gerontology and the biology of aging.
- To guide the whole process of bringing the healthy longevity message to the wider public and set standards for the market through effective marketing of the sector assembling researchers, policymakers and insurance industry.

FOR INVESTORS AND THE FINANCE SECTOR

- To promote and spread the idea of sustainable profits in terms of financial return and social benefits.
- To establish how to measure success for the sector and stakeholders, and with what benchmarks and time intervals to assess this.

FOR THE INTERNATIONAL INSTITUTE OF LONGEVITY

- To create a knowledge repository on longevity and promote it to society and investors.
- To use the current momentum to become a platform of communications for a variety of stakeholders from business, researchers, governments and individual consumers.
- To establish a Board of Counsellors that would hold regular meetings and develop ongoing recommendations.
- To continue bi-annual Longevity Roundtables facilitated by the Vaduz Roundtable Foundation attended by major players including industry leaders, scientists, governments, regulators and big pharmaceutical companies.
- To facilitate creating and financing innovative businesses and start-ups in the longevity sector in Europe through a Longevity Accelerator.

Definitions

AGING – cumulative damage arising as side effects of the organism's normal metabolic processes.
HEALTHY AGING – is defined by the WHO as the process of developing and maintaining the functional ability that enables well-being in older age. Functional ability is about having the capabilities that enable all people to be and do what they have reason to value.

S
STRENGTHS

Dynamic development of the longevity sector and geroscience within the last couple of years due to breakthrough discoveries in research on aging.

Exponential growth in interest from venture capitalists.

Several therapeutics have been successfully tested on animals offering very promising potentially longevity-extending results (NAD+, mTOR inhibitors, rapamycin etc.).

Several interventions are currently in first-ever human clinical trials for potentially longevity-extending indications. (senolytics, metformin, etc.).

In Europe: a strong tradition of healthy lifestyle and fresh food that are part of many people's everyday life, which makes it easier for them to be inclined toward the idea of a healthy lifespan.

Great potential for expansion in existing European research institutions (universities and R&D centers) and for increasing scientific funding from the EU.

In 2019, the World Health Organization (WHO) introduced an extension codeICD 11 to the International Classification of Diseases (ICD) for "age-related," which brings the industry closer to classifying aging as a disease. FDA appears poised to follow suit.

W
WEAKNESSES

Lack of understanding of the idea of healthy longevity among the public, medical profession and policymakers. Many view aging in a totally negative light rather than as a fruitful period of life that can be appreciably enhanced.

Governments and insurers currently do not classify aging as a treatable condition, which results in a lack of funding and difficulty in researching, developing and prescribing therapeutics that could mitigate the aging process.

The lack of scientifically validated biomarkers of aging prevents an assessment of the effectiveness of potentially age-mitigating treatments.

Centers devoted to research on aging are dispersed and mostly in the U.S. Insufficient coordination of aging research in Europe.

Insufficient understanding for the sector in the financial industry and low appetite for risk among some institutional investors.

O
OPPORTUNITIES

New breakthroughs in our understanding of the biology of aging and age-related diseases will help to extend healthspan and the quality of life.

Increased understanding that preventive health – moving from "sick care" to health care - is the only solution for meeting retirement and health costs in the near future.

Changing the outdated perception of the 65-year age limit. Mobilizing activities including career reorientation and start-ups for the generation starting at 55+.

Introducing new legislative measures supporting pension age flexibility and working schemes for older generations may result in high savings in state and regional budgets.

T
THREATS

Mental obstacles - most people still associate living longer with being in a dramatically reduced state of health. Education is needed to overcome this.

Widespread belief that rejuvenation technologies will be available only to the wealthy and will promote further societal inequality.

Potential for the reputation of the sector to be negatively impacted by fringe actors who are making baseless promises and raising ridiculous expectations.

VADUZ ROUNDTABLE

INTERNATIONAL INSTITUTE OF LONGEVITY

www.iiol.eu
www.L-institute.com