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Live Longer or Healthier? The Science That Is Making Both Possible

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Foreword

The technological leaps that have shaped our modern health-care systems are astonishing. From antibiotics to stem-cell therapies, our ingenuity and determination to live longer and better lives have dramatically changed human experience over the past century.

While the gradual decline of ageing has been seen as inevitable in the past, recent scientific advances suggest that it doesn't have to be this way.

Age is one of the biggest risk factors in hospitalisations or death caused by many of the chronic illnesses plaguing developed nations, including cardiovascular disease, cancer and dementia. Today, the majority of medical research tackles each of these age-related illnesses individually and in turn. Important breakthroughs often deliver an extra two or three years of healthy life, only for patients to then fall victim to yet another age-related disease.

Yet, what if we could instead focus on tackling ageing itself?

By uncovering the underlying mechanisms of ageing, we are on the cusp of being able to delay the onset of age-related conditions and confront the causes of degenerative diseases. In fact, by targeting the biology of ageing, healthspans and lifespans have already been extended in numerous animal models, with some of the related drugs already in human use.

Timing is of the essence: major demographic shifts mean that the economic and health-care structures created in the 20th century will not be able to support future generations. The economic issues presented by ageing populations are existential in scale and, arguably, second only to the pressing climate challenges we face.

Yet this risk also presents an opportunity. The prize for radically extending healthy lifespans is enormous, both economically and in terms of public health. This "longevity dividend" is potentially so significant that we must take immediate steps to accelerate efforts to address age-related diseases.

Tackling the root causes of ageing offers great promise. This paper highlights some of the most exciting innovations in longevity and why this field will be a major source of innovation during this century. It sets out clear rationale for why policymakers must act now to seize this opportunity, as well as describing the most pressing action for governments globally. By delaying the onset of age-related diseases, we have the opportunity not only to create a more positive, grounded and equitable vision of an ageing society, but to deliver healthier lives for each of us – a goal that's surely worth pursuing.

Dr Nir Barzilai, Director, Institute for Aging Research, Albert Einstein College of Medicine and Scientific Director of the American Federation for Aging Research

Introduction

One of humanity's greatest success stories of the past century is the increase in global life expectancy as a result of the social and medical advancements that have dramatically improved basic living conditions and reduced vulnerability to infectious diseases.

However, longer lives haven't fully translated into healthier lives, and as we grow older the likelihood that we will live with debilitating chronic illness rises significantly. In most advanced economies, healthy life expectancy (HLE, sometimes referred to as Health-Adjusted Life Expectancy) has not increased at the same pace as overall life expectancy (LE), and the years that people spend living with disability or disease have risen steadily. In the UK, the situation is alarming. The latest ONS figures show that men can now expect to live 16.5 years in poor health, and women a staggering 19.8 years.

Beyond unacceptable personal suffering, this places extreme pressure on both health-care systems and the economic models of advanced economies. The problem of ageing populations, combined with decreasing birth rates, has been described by demographers and economists as a societal challenge similar in scale to climate change, with enormous impacts looming for many nations if left unaddressed.

However, a new frontier of science is emerging – longevity research, also referred to as geroscience – that is helping us understand the underlying biological mechanisms of how and why we age, with the potential to develop treatments that delay, prevent or even reverse the onset of ageing and multimorbidity. In short, the nature and speed of the ageing process, and the aches and pains that accompany it, may not be inevitable. If we can successfully intervene to ensure ageing is healthy for as long as possible, then the potential gains in personal, public and economic health would be enormous.

In this paper, we examine the public-health and economic imperative to act, look at some of the most promising areas of innovation in longevity research across academia and industry, and propose practical actions that governments should take to invigorate this critical but under-resourced area of science.

Given the profound implications, we believe governments should set ambitious targets: the UK and other advanced economies should aim for **"30 in 30"** – to increase HLE by 30 years (to approximately 95 years) by 2050.

While our work is international in scope, we also include a case study on how the UK can play a global leadership role in longevity research and development. With its world-leading academic institutions, strong life-sciences industry, access to vast NHS data sets and a global financial hub in London, the UK is already primed to become a global leader in this nascent field.

Our discussion is not exhaustive; many things contribute to longer, healthier lifespans, but here we focus on some of the most exciting areas of innovation that we believe can rapidly accelerate progress – if policymakers are bold enough.

The Economic and Public-Health Imperative

In most advanced economies, the younger, working population has typically supported the older, non-working population through taxation and social security to enable the provision of pensions and health and social care in older age. This worked in the 20th century, but large demographic shifts are placing increasing strain on this model. The difference between LE, HLE and the pensionable age has grown significantly over recent decades and is projected to continue to do so, placing unsustainable pressures on pension and health-care systems worldwide.

Figure 1 – Healthy life expectancy by country (1990–2016)

Source: Our World in Data, Healthy Life Expectancy, 1990–2016

In the UK, the latest estimates from the ONS show that the government's pension liabilities grew by more than 20 per cent between 2015 and 2018 alone, and now total £6.4 trillion (almost two-and-a-half times GDP). Meanwhile, the Resolution Foundation has recently estimated that the NHS alone will account for almost 40 per cent of public spending in the UK by 2025 (up from 28 per cent in 2004).

Figure 2 – Share of GDP attributed to total health-care expenditure in the UK, 1997–2018

Source: ONS health-care expenditure (UK health accounts, 2018). This covers health-related elements of care provision including where a "substantial proportion of the service involves support with based activities of daily living" and "services provided in residential and nursing homes" (ONS). Broader social-care support is not included in the UK health accounts.

The situation is similar across much of the Organisation for Economic Cooperation and Development (OECD). A recent study on trends in age-related disease burden and health-care utilisation in Italy (where life expectancy is currently the highest in Europe) found the prevalence of multiple chronic diseases and the use of health-care services have increased considerably over time among older adults, accounting for 20 per cent of the total Italian health-care budget in 2014. Without intervention, the number of people living with chronic conditions is projected to increase sharply as the total population over the age of 65 increases. Moreover, biomedical advances are making health-care interventions increasingly more sophisticated and expensive in comparison to those used by previous generations.

Figure 3 – Percentage of population aged 65 years or over (upper-middle-income countries)

Source: https://population.un.org/wpp/Download/Standard/Population/

Figure 4 – Projected percentage of population aged 65 and over by country, 2020–2100

Source: UN population percentage by age (probabilistic projections)

This is placing an enormous and growing burden on societies, creating challenges for how we help people to live healthy and active lives in their older years, how we support older people when they do need care and how we pay for it. This has been brought into sharp focus in the UK with the recent rise in National Insurance contributions to support growing social-care needs. It is clear that we need to develop longer-term strategies and invest in research and technology to reduce this increasing and overwhelming demand.

Innovation in longevity research offers a promising potential solution. Scientists are beginning to understand the molecular processes of ageing, which are increasingly thought to contribute to a variety of chronic illnesses. If these mechanisms can be fully understood and targeted, it gives hope that we can delay the onset of ageing and multimorbidities, enabling us to live more healthily for longer, and therefore reducing health- and social-care burdens. Moreover, recent economic analysis has estimated that targeting ageing through investment in longevity research and policies could not only help alleviate escalating health-care costs but also create significant additional economic value.

Research from the AARP and Oxford Economics has shown that the 50-plus cohort remains a powerful force in driving economic growth and value. This age group's contributions, including both the products and services they purchase directly and the further economic activity this spending generates, are collectively known as the "longevity economy", which amounted to $7.6 trillion in 2015. The value of keeping this cohort healthier and more productive for longer would make a significant contribution to advanced economies.

Economists have estimated that the economic value of compressing morbidity and increasing healthspans by taking a holistic approach to targeting the causes of ageing rather than looking at individual diseases in isolation is likely to be in the trillions. As the ageing populations of advanced economies become ever more burdensome on the state, taking action to radically extend healthspans is an opportunity that policymakers can no longer afford to ignore.

Signs of Progress

Understanding the Biology of Ageing

Fortunately, progress is being made. The field of longevity has taken significant strides over the past two decades, and there have been major breakthroughs in our basic understanding of the biology of ageing, offering insights into how we might combat it.

At its most fundamental level, ageing is a biological process or – more accurately – the cumulative effect of multiple processes occurring in parallel. It happens at both a molecular-cellular level and at a systems level, where entire organs can lose their function over time, and is influenced by both environmental and genetic factors.

Researchers have already begun to identify key hallmarks of ageing (see Figure 5). While there is not yet consensus around the number, hierarchy and order of importance of these hallmarks, there is general agreement that certain processes – such as cellular senescence, stem-cell exhaustion and macromolecular dysfunction (telomere shortening and damage to DNA and proteins) – are important components of the overall ageing process. These promising insights have already helped identify molecular targets, and offer hope that the development of treatments to delay, prevent or even reverse the onset of ageing may be within reach in the not-too-distant future.

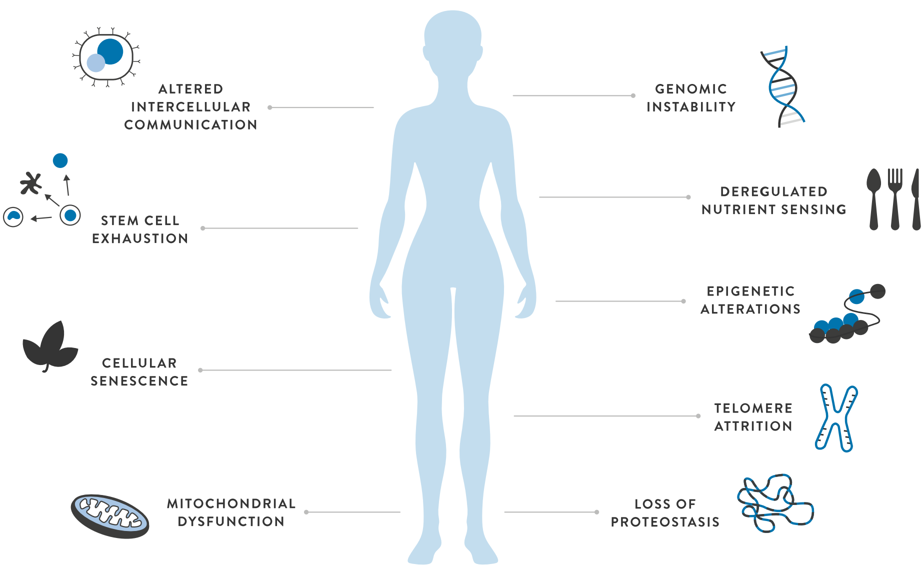
Longevity in a Pill?

One of the most promising areas of progress has been the development of senolytics – a class of drug that seeks to specifically target senescent cells. Cellular senescence is a process by which cells stop normal division and undergo significant structural and behavioural changes. This functions as a mechanism to check uncontrolled growth (as seen in cancers) and, in healthy contexts, can also perform important roles in normal development and tissue repair. However, more recently, chronic senescence has been shown to be associated with ageing and age-related disease, and the accumulation of senescent cells with age, particularly at causal sites for different chronic disorders, has been demonstrated in a variety of model organisms. This appears to be, at least in part, caused by abnormal cellular secretion patterns that can lead to localised inflammation and result in collateral damage and the death of neighbouring healthy cells.

Although the mechanism through which senescent cells contribute to ageing is not fully understood, they represent a credible target to slow holistic ageing. A number of drugs that aim to eliminate senescent cells have already been developed, including dasatinib, quercetin, fisetin and navitoclax. In preclinical models , senolytics have been shown to delay or alleviate a variety of age-related conditions and, promisingly, clinical trials are already underway to test the effectiveness of candidate drugs in humans.

Building on senolytics, several other molecular pathways that appear to play a role in ageing have been identified. These pathways are usually activated by healthy exercise and diet, but researchers are discovering a new class of drugs that mimics and, in some cases, surpasses the benefits of such practices. Metformin remains one of the most promising candidates. Originally created to treat type-2 diabetes, metformin has been shown to favourably influence inflammation and cellular senescence, both of which are associated with the development of age-related disease. A randomised controlled clinical trial is currently in development – titled Targeting Aging with Metformin (TAME) – to test the use of metformin in humans, with a series of six-year clinical trials at research institutions across the US. The hope is that the study will result in clear clinical evidence to identify the efficacy of the drug in addressing the cellular processes linked to ageing; fundraising is currently underway to begin the trial.

Figure 5 – Hallmarks of ageing



Source: https://www.juvlabs.com/aging-research/hallmarks-of-aging

Rapamycin, which is involved in a different pathway, has also emerged as a potential drug candidate. A strong body of evidence is emerging showing that rapamycin is effective in preventing several age-related conditions including cancer, cardiac disease and brain ageing in rodent models. The drug affects mTOR signalling, which influences a range of age-related processes such as cellular senescence and stem-cell function. Researchers at UCLA have recently crowdfunded almost $200,000 for the first trial into the use of rapamycin for human ageing. The PEARL trial will enrol 200 participants, tracking the impact of four different rapamycin-dosing regimens over 12 months. An early study is also underway looking at the effectiveness of rapamycin in treating Alzheimer's disease, with researchers suggesting the drug could target the multiple pathways that appear to be disrupted in dementia.

If the candidate drugs currently going through clinical trials prove to be effective and safe, significantly extending health and lifespans through medical interventions may be closer than we think. However, this is just the tip of the iceberg and, as we increase our understanding of the biology of ageing, more molecular targets will be uncovered, offering the potential for the development of more novel drugs and treatments.

Advances in Genomics, AI and Gene Editing

Recent advances in genomics and artificial intelligence (AI) present profound opportunities to do just this. Epidemiology and microbiology studies have played an important role in establishing the known hallmarks of ageing, but genomics and broader multi-omics studies offer a more systematic approach to revealing the underlying genetic factors and cellular pathways involved in ageing. Meanwhile, AI brings powerful analytical capabilities to the large data sets these studies generate to help uncover meaningful insights more quickly.

Efforts to understand the cellular mechanics of ageing through genomics have increased considerably in recent years. Several whole-genome studies have already identified hundreds of genetic elements associated with abnormally long or short lifespans in various model organisms, including humans. Meanwhile, online databases, such as Human Ageing Genomic Resources and GenAge, have also emerged, providing platforms and tools for researchers to share information and analysis to accelerate progress.

A study from the UCL Institute for Healthy Ageing, published earlier this year, used a large-scale lifespan assay to uncover hundreds of new genes associated with ageing in yeast, including 46 genes also found in humans, but which are completely uncharacterised. This serves to demonstrate that there is still much we don't yet understand, but also highlights the enormous potential that exists to discover new drugs and to develop new treatments.

However, in a world where medicine is becoming increasingly personalised, we need to understand not only the general mechanisms of ageing, but also how ageing may manifest differently across various subpopulations and even at the individual level. Researchers are already beginning to investigate this and have recently used deep, long-term, multi-omic profiling to begin to define "ageotypes" (subpopulations that exhibit different mechanisms of ageing) and personal markers of ageing.

While our lifestyle choices will undoubtedly have a huge bearing on how quickly we degenerate, in an era in which we can consciously choose to live healthier lives, genetic factors will also increasingly differentiate those of us destined to live longer. While not yet close to clinical settings, recent advances in gene editing – particularly ever more sophisticated CRISPR technologies (a gene-editing technique, short for "clustered regularly interspaced short palindromic repeats") – also offer the future promise of being able to overcome the inheritable traits that can leave us more predisposed or susceptible to ageing.

Measuring Ageing

What gets measured gets managed, and as well as unravelling the biological mechanisms of ageing, we also need to be able to accurately measure its progression. This is important for two reasons.

First, in order to determine the effectiveness of candidate treatments in clinical trials and whether new medications are to reach health-care settings anytime soon, we need more immediately measurable readouts, rather than relying on the impact on lifespan. Secondly, the genetic and environmental factors that contribute to our ageing are unique to each of us, so our biological age may be different from our chronological age, giving a new and more literal meaning to the expression "young at heart". Being able to determine this difference is critical to understanding how our environmental and lifestyle choices impact our biological age.

Reliable markers of biological age (ageing biomarkers) are therefore needed to more rapidly deliver new therapies, and to help understand and address the differences in variability in ageing between individuals. Progress is being made on this frontier too. Most significantly, researchers have uncovered an array of epigenetic markers that strongly correlate with biological age. While these so-called epigenetic clocks give a relatively immediate and accurate approximation of ageing, there is still a critical need for a more diverse range of ageing biomarkers to provide flexible and robust estimations of biological age.

Technology may provide part of the solution. Personal markers of ageing are also at the heart of the next generation of wearables, with biomedical data being used to predict the body's cellular age and biological resilience more accurately. By monitoring sleep, heart rate, movement and other health factors, researchers are now able to offer an assessment of biological age. It is hoped that the volume of data being generated – driven by the decreasing cost of many lifestyle wearables and developments in AI and machine learning – will enable us to receive personalised feedback on the lifestyle choices we make, which will unlock increased healthy life expectancy.

Regenerative Medicine

Beyond progress in our understanding of the genetic and molecular bases of ageing, advancements in combatting age-related degeneration at a systems level have also been made in recent decades. Regenerative medicine focuses on developing methods to regrow, repair or replace damaged or diseased cells, tissues or organs. This includes treatments such as stem-cell therapy, tissue engineering and even the creation of artificial organs. Some treatments are not new – the first heart transplant took place in the 1960s. However, in the US alone, there are 114,000 people on the waiting list for an organ transplant and, on average, 20 people die every day from the lack of an available organ. Innovations in regenerative medicine could save lives and improve countless others, not to mention help to alleviate some of the enormous costs.

The ability to regenerate cells varies across populations and species. Some organisms, like the freshwater hydra, can regrow their entire body from a piece of tissue in a few days. Humans have some regenerative capabilities, such as being able to knit fractured bones back together, but our species is also limited by cell type and age. Building on advances in genomics, scientists are exploring how to induce regeneration of muscle cells and the cells of certain vital organs, such as the heart, through gene therapy and genetic engineering in order to address the complications that often accompany old age. Researchers are even starting to see the possibility of regenerating whole organs through cellular therapy. Following a study in which cells injected into the lymph nodes of animals with diseased livers successfully resulted in the growth of mini-organs that supported or restored normal liver function, one biotech startup is set to conduct clinical trials in humans later this year. Similarly, a recent study appears to show that using human-growth hormone can rejuvenate the thymus and reverse the body's epigenetic clock.

Due to transplant shortages and time-sensitive scenarios where a patient's immune system rejects donor cells or tissue, tissue engineering has increasingly become an area of focus in regenerative medicine. Tissue engineering involves combining cells with a scaffold and growth factors to create artificial tissues. Tissues require support for their formation, and the scaffold assists with this through structural support, promoting attachment, proliferation and differentiation. Developments in tissue engineering are already paving the way for artificial organs: four women were recently able to regain full sexual function after the successful implantation of lab-grown vaginas created from their own cells.

Implications for Policy

Advances in technology are unlocking our understanding of ageing at an accelerating pace. Progress in mapping the fundamental biology of ageing, identifying new molecular targets, genomics and AI all offer hope of living healthier lives for longer. The potential prize of radically extended healthspans, both in terms of the quality and quantity of life and the impact on economic outlook, is vast and within reach, but only if policymakers are bold enough to seize the opportunity. There are a number of immediate actions that advanced economies can take to progress this agenda, starting with the following steps:

- **Set ambitious, long-term targets:** Policymakers need to think more realistically about the magnitude of the challenge that ageing represents and more radically about finding solutions. To do this, governments must set ambitious, long-term targets in a similar vein to climate goals to drive progress. There is consensus among experts that we already have the knowledge and technologies to achieve a **"30 in 30"** target – in other words, to increase HLE by 30 years (to approximately 95 in most advanced economies) by 2050, if the right policies and technologies are implemented. It is an ambitious but achievable long-term aim. Governments also need to set short-term targets so they can measure progress against, and be held accountable for, these longer-term goals.
- **Ensure longevity is at the heart of life-sciences strategies:** To be meaningful, targets must also be accompanied by comprehensive strategies and roadmaps. As part of this, the life-sciences strategies of governments should push for a greater emphasis on longevity research. This should include specific efforts to foster and fund both basic and translational research into holistic degeneration, in addition to the current model of focusing solely on individual chronic diseases. Areas of great opportunity and promise, but which require sufficient investment, are: exploration of the known hallmarks of ageing; improving our understanding of the molecular basis of ageing through large-cohort, whole-genome association studies; defining new ageing biomarkers; and developing personalised multi-omic ageing profiling.
- **Employ innovative funding models to accelerate progress:** As well as increasing direct funding for longevity research, governments should also consider innovative funding models to drive progress faster. Fast Grants – which can greatly accelerate the allocation of resources to researchers, as we have seen during the pandemic – and prize competitions are two options that have proven effective, but these need not be exhaustive.
- **Incentivise innovation and equity in the private sector:** The interest of private industries in longevity is growing but still at an early stage. Governments can accelerate its development through targeted interventions and by investing in publicly funded basic research to build foundational knowledge. And while the private sector has an important role to play in longevity innovation and investment, market forces don't always translate to equitable outcomes. This means that the public and private sectors must work together to ensure that the most innovative ideas are explored and that any breakthroughs are shared so they can benefit the greatest number of people.

- **Model the fiscal and economic value of increasing HLE:** As we look to the next century, advanced economies are likely to face massive demographic change, requiring new economic models to accommodate ageing populations. At the same time, unless action is taken, health-care systems will continue to be burdened by the ever-increasing cost of managing multiple chronic diseases. These combined pressures create significant social, fiscal and economic risks, but if policymakers tackle them in the right ways, the potential economic upside could be enormous. While some countries, such as the UK, have begun to calculate the long-term fiscal risks associated with ageing populations, few (if any) governments have modelled the economic benefits of targeting ageing to increase HLE in a comprehensive way. Even modest increases in HLE could be worth trillions in economic value globally. However, this needs much more thorough analysis at the national level and, given regional and socioeconomic disparities in LE, HLE and economic conditions, this should expand to include state and regional analysis to ensure equitable outcomes.
- **Facilitate clinical trials:** As governments reflect on the pace of progress for clinical trials in response to Covid-19, they should consider specifically how they might better facilitate clinical trials in longevity research. Regulators need to make a concerted effort to smooth the pipeline between pre-clinical and human studies; an overly complex process slows progress and blocks commercial routes, disincentivising investment from pharmaceutical companies and others. For example, not classing ageing as a disease has been an obstacle. The World Health Organisation's decision in 2018 to add an extension code for "ageing-related" to the International Classification of Diseases was a crucial step in recognising the importance of research focused on ageing. While helpful, not every country's regulatory body has done the same, and standard practice requires that official classification as a disease is needed in order to begin development of drugs and therapies. Regulations around ageing biomarkers have similarly been challenging for longevity researchers due to a lack of consensus and standard requirements around endpoints. Regulators could unlock progress by giving researchers the ability to use multiple biomarkers as proxies for measuring ageing. Alternatively, an easier step, without completely having to overhaul clinical trials, could be allowing the endpoints of studies to be redefined and proxy biomarkers used.
- **Change and lead the ageing narrative:** Policymakers should reframe ageing as an existential issue, with significant economic and public-health consequences, but one that can be addressed. The political and policy communities must better champion the value to the public purse and to families of addressing multiple morbidities and then communicate the enormous risks to society if left unconfronted. An important part of this, which will drive progress, is to help longevity research gain further credibility and to be adopted by academic, university and medical communities, where its value remains underestimated. To build trust, policymakers need to articulate a positive, grounded and equitable vision for an ageing society, which focuses not only on managing complex health conditions but also on the potential to prevent them altogether.

Putting Britain at the Forefront of Longevity Research: A Four-Point Plan

A few countries around the world are beginning to become more active in the longevity space. The US is home to several leading longevity research labs while the government in Singapore is focused on facilitating clinical trials, encouraging some of the most exciting companies in longevity research to adopt a base there.

The UK has a unique opportunity to position itself at the forefront of longevity research. The vast centralised data sets available via the NHS offer significant opportunities in enabling us to better understand the biology of ageing. The UK Biobank – a large-scale biomedical database containing genetic and health information from half a million volunteers – also offers great opportunities to identify ageing biomarkers and support drug-discovery efforts, and is already being used by some leading longevity researchers.

Building on this success, there are four "no-regrets" steps the government should take immediately to place the UK on a competitive footing in this emerging field.

1. Publicly commit to delivering "30 in 30". The government's current target aims to add five healthy, independent years to people's lives by 2035. This is insufficient in both scope and ambition. The UK should instead set out to deliver "30 in 30": to increase healthy life expectancy by 30 years by 2050. This is ambitious but achievable, and can be delivered by tackling the molecular causes of ageing, using personalised data on individuals' markers of ageing and more advanced interventions to tackle multimorbidity, which we expect to reach market during the coming decade.

2. **Significantly increase funding and explore innovative funding models for longevity research.** In the UK, there are currently no accurate figures for the amount of public funding directed towards ageing research per capita, per annum, although researchers estimate it can be measured in pence rather than pounds. By contrast, we spend around £2.80 per person on cancer research annually. Longevity research should be at the core of the UK's life-sciences research funding and, as such, requires far greater levels of investment than estimates suggest is currently being spent.

3. **Give the NHS first refusal on publicly funded longevity therapies.** Government should ensure that novel therapies developed in publicly funded labs retain a public benefit when taken to market. Policymakers should explore novel ideas like a National Therapeutics Service to ensure the NHS has first refusal on any ageing therapies that emerge through publicly funded longevity research in universities.

4. **Model the fiscal and economic value of extending life and healthspans at national and regional levels.** While the UK has begun to calculate the long-term fiscal risks associated with ageing populations, it hasn't publicly modelled the economic value of targeting ageing to extend life and healthspans. Work by researchers from the London Business School, University of Oxford and Harvard Medical School, published in the journal Nature Aging, offers a model for how longevity-focused interventions could be quantified. HM Treasury should conduct equivalent modelling to assess the economic value at stake.

Conclusion

Longevity research already offers a real chance to extend the "healthy" portion of people's lives, but the future is filled with even more transformative possibilities. As advances in our understanding of the biology of ageing, gene therapies, drug discovery and regenerative medicine evolve at pace, it is likely that we will soon be able to accurately track and reduce our biological age, regenerate ageing tissue and perhaps prevent cell senescence, potentially enabling us to live healthily until the age of 95 by 2050. Driven by a new frontier of research, the coming decade has the power to truly transform both the way we live and the way we age, with profound implications for each of us. Political leaders must seize this opportunity and the great prize at stake.

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