Technologies series

Life extension

Life extension aims to extend dramatically humans' healthy lifespan; but current approaches lack evidence.

Live long and prosper

What it is

The extension of human life beyond the customarily-recognised maximum human lifespan.[1]

How it works

The idea of life extension regards biological ageing as a disease to be treated,[2] and aims to extend the 'healthspan'.[3] There are various processes associated with ageing;[4] including systemic inflammation,[5] genomic[6] and epigenetic damage,[7] telomere shortening,[8] metabolic dysfunction,[9] and accumulation of senescent cells.[10] Although these broad processes are recognised, the precise molecular mechanisms have yet to be unravelled, making the design of treatments difficult.[11]

Approaches

There are a number of suggested approaches to treat ageing, each with varying degrees of supporting evidence.[12] However, at present no approach has materially lengthened the healthy human life span; or restored or maintained cognitive and physical functionality:

1. **Calorie restriction.** Dramatically reducing calorie intake has been shown to extend life significantly in animals.[13] Research is focused on determining the responsible molecular mechanisms, and whether they can be activated using small molecule drugs.[14]
2. **Anti-senescence drugs.** As ageing progresses some cells become less functional (senescent)[10] and can cause damage: treatments to clear them could limit this damage.[15]
3. **Parabiosis.** Linking the circulatory systems of young and old mice has shown improvements in physiological parameters in the old, and worsening in the young.[16]
4. **Anti-ageing drugs.**[17] Predominantly drugs that mimic the effects of calorie restriction, these include; metformin,[18] rapamycin,[19] spermidine,[20] and resveratrol.[21]
5. **Stem cells.** Long-hyped, stem cells are a promising class of treatment with the potential to rejuvenate tissues and organs, but which require more evidence in humans.[22]
6. **Genetic editing.** Genetic editing could prevent certain ageing processes, but faces ethical, regulatory, and most importantly practical, obstacles given that ageing is multi-factorial.[23]
7. **Cryonics.** It is hoped that, by freezing the human body or head, it can at a later date be thawed and brought back to life once medical science has advanced sufficiently.[24]

Implications and issues

The field of life extension is a relatively new field, and seems fraught with over-promise. However, distinct lines of ageing research are taking shape, and the interest in slowing or reversing it is high. There are a great number of considerations:

- **Overinterpretation.** Many findings from ageing research in animals have not translated to humans – predominantly, the effectiveness of treatments and interventions.[25]
- **Clinical endpoints.** Given the length of the human lifespan, scientific studies to assess the impact of interventions on lifespan are almost impossible.[26] Surrogate markers are required.[27]
- **Regulation.** Given that ageing is not widely recognised as a disease, treatments will need to demonstrate other improvements in order to receive approval from medical regulators.[28]
- **Double-edged outcomes.** It may be that inventions that prevent cells form ageing increase the risk of developing cancer, if pre-cancerous cells are maintained instead of removed.[29]
- **Potential market.** It is an attractive business opportunity, given that ageing affects everyone.
- **Medical costs.** Ageing is the largest risk factor for chronic diseases, so treating it would reduce their burden dramatically, and go a long way to addressing issues of shifting demographics.[30]
- **Social inequality:** If possible only through costly means, life extension could exacerbate social tensions and inequalities.

Currently there is a lack of scientific evidence that life extension approaches have appreciable effects on lifespan in humans. However, many distinct processes are under active investigation. It seems to have potential to bring a range of benefits.■

The sidebar quote is the Vulcan salute from Star Trek, made famous by Leonard Nimoy's character Mr Spock.

[1] The person known to have lived longest was Jeanne Calment, who died in 1997 at the age of 122. However, as can be expected, it is difficult to put an accurate number on the maximum human lifespan. Present estimates range from 115 to 125, but limits to human lifespan are intensely disputed. Demographic studies suggest that, after a given age, the risks of dying plateau (but remain high), which could indicate absence of a limit. However, these studies are subject to small sample sizes; and perhaps the more important number is the likelihood of reaching an incredibly old age. See: Barbi, E., et al., 2018. The plateau of human mortality: Demography of longevity pioneers. *Science* [e-journal] https://doi.org/10.1126/science.aat3119 (paywall) and Dong, X., Milholland, B. & Vijg, J., 2016. Evidence for a limit to human lifespan. *Nature* [e-journal] Available at: https://doi.org/10.1038/nature19793 (paywall) and associated editorial, Olshansky, S., 2016. Measuring our narrow strip of life. *Nature* [e-journal] https://doi.org/10.1038/nature19475.

[2] The view of the constellation of features associated with ageing as a disease, proposed by numerous researchers, is relatively new, and is not accepted by the broader medical community. However, it is gaining traction with those who believe that human health consists of a complex network of intertwined systems that fail in a cascading fashion as people age. See, Barzilai, N., 2018. Aging as a Biological Target for Prevention and Therapy. *Journal of the American Medical Association* [e-journal] https://doi.org/10.1001/jama.2018.9562 (paywall) and Partridge, L., 2018. Facing Up to the Global Challenges of Ageing. *Nature* [e-journal] https://doi.org/10.1038/s41586-018-0457-8 (paywall).

[3] Healthspan refers to the length of healthy life expectancy. In the past decade this has become distinguished from increasing lifespan: nowadays, the elderly survive for longer than used to be the case, but with multiple chronic health conditions. The key aspects of longevity research are outlined by the trans-NIH Geroscience Interest Group in: Kennedy, K.B., et al., 2014. Geroscience: Linking Aging to Chronic Disease. *Cell* [e-journal] https://doi.org/10.1016/j.cell.2014.10.039 and Crimmins, E. M., 2015. Lifespan and Healthspan: Past, Present, and Promise. *The Gerontologist* [e-journal] https://doi.org/10.1093/geront/gnv130

[4] An influential review on the subject outlines 9 hallmarks that occur commonly in ageing organisms, and represent mechanisms that may be altered in order to ameliorate ageing. See: López-Otín C., et al., 2013. The hallmarks of aging. *Cell* [e-journal] https://doi.org/10.1016/j.cell.2013.05.039.

[5] A recently appreciated phenomenon is that of '*inflamm-aging*', which refers to the increased levels of systemic inflammation detected in older individuals when compared with younger. This is similar to the inflammation associated with injury or infection, but less intense. However, it can have negative consequences for the organism, such as increased risk of developing a chronic disease such as diabetes, chronic kidney disease, cardiovascular disease, neurodegenerative disease, or cancer. See, Franceschi, C., et al., 2018. Inflammaging: a new immune–metabolic viewpoint for age-related diseases. *Nature Reviews Endocrinology* [e-journal] https://doi.org/10.1038/s41574-018-0059-4 (paywall).

[6] Our genome is thought to be 10-30% responsible for determining the length of our lifespan. In addition to those we inherit, as humans age our cells accumulate genetic mutations in their genomes, purely as a function of random errors made during the replacement process. Older organisms have a higher number of mutations, with a correspondingly higher chance for these mutations to damage the functioning of the cells. In addition to this, a number of diseases of accelerated ageing involve damage to the genome, indicating its importance to the processes of ageing. See, Melzer, D., Pilling, L.C. & Ferrucci, L., 2020. The genetics of human ageing. *Nature Reviews Genetics* [e-journal] https://doi.org/10.1038/s41576-019-0183-6 (paywall) and Burla R., at al., 2018. Genomic instability and DNA replication defects in progeroid syndromes. *Nucleus* [e-journal] https://doi.org/10.1080/19491034.2018.1476793.

[7] Epigenetic modifications are alterations to our genomes which do not change the letters of the genome, but rather the way in which it is read, by 'flagging' certain sections with additional molecular markers. These occur throughout our lives, and can be subsequently inherited by offspring. It has been determined by researchers that the degree of modification correlates relatively well with biological age, as opposed to chronological age. This provides some degree of an estimate of healthspan. However, the reasons for this are not yet known, and it also remains unknown whether it is possible to slow biological ageing by directly targeting age-related DNA methylation levels. See, Horvath, S., & Raj, K., 2018. DNA Methylation-Based Biomarkers and the Epigenetic Clock Theory of Ageing. *Nature Reviews Genetics* [e-journal] https://doi.org/10.1038/s41576-018-0004-3 (paywall) and Zhang, W., et al. 2020. The ageing epigenome and its rejuvenation. *Nature Reviews Molecular Cell Biology* [e-journal] https://doi.org/10.1038/s41580-019-0204-5 (paywall).

[8] The 23 chromosomes that comprise our genome are all capped with lengths of repeating DNA sequences, called telomeres. These chromosome-capping telomeres are thought to protect the end of the chromosomes from deterioration. As we age these telomeres shorten, potentially increasing the chances of damage to our genome and subsequent reduced functioning of our cells. However, research has questioned the importance of telomere length to age-related decline. In an analysis of 261,000 members of the UK Biobank, people with longer telomeres did not have improved health in old age. See, Kuo, C-L., 2019. Telomere length and aging-related outcomes in humans: A Mendelian randomization study in 261,000 older participants. *Ageing Cell* [e-journal] https://doi.org/10.1111/acel.13017.

[9] Metabolism is the process of producing energy and building blocks to sustain life. Many genes relating to growth and metabolism have been associated with ageing. Although most research in this context has been carried out in animals, the fundamental pathways are the same in humans. See, Finkel, T., 2015. The metabolic regulation of aging. *Nature Medicine* [e-journal] https://doi.org/10.1038/nm.3998 (paywall).

[10] As the body ages its old cells divide to form new ones. However, mutations can accumulate in cells as they divide, and they can eventually become cancer cells. As an anti-cancer measure, cells can enter into a sort of static state of non-division known as senescence. These avoid the risk of cancer, but release a complex cocktail of molecules that cause inflammation and damage nearby cells. Senescent cells have been linked to a number of health conditions associated with ageing, including diabetes, kidney disease, and many cancers. Research carried out in mice has demonstrated that if these senescent cells can be removed then certain aspects of ageing can be improved, such as the likelihood of developing cancer, kidney function, and abnormalities in heart and fat tissue. However, not all aspects of ageing were improved, including declines in motor performance, muscle strength, and memory. See, Gil, J., & Withers, D., 2016. Out with the old. *Nature* [e-journal] https://doi.org/10.1038/nature16875 for the editorial, and for the original research article see, Baker, D. J., et al., 2016. Naturally-occurring p16Ink4a-positive cells shorten healthy lifespan. *Nature* [e-journal] https://doi.org/10.1038/nature16932 (paywall). Further background on senescence is provided by the following, Lee, S., & Schmitt, C.A. 2019. The dynamic nature of senescence in cancer. *Nature Cell Biology* [e-journal] https://doi.org/10.1038/s41556-018-0249-2 (paywall).

[11] A number of processes correlate with ageing (See Endnote 4), but precise mechanisms have not yet been defined in sufficient detail to generate treatments. See, de Magalhães, J.P., Stevens, M., & Thornton, D., 2017. The Business of Anti-Aging Science. *Trends in Biotechnology* [e-journal] https://doi.org/10.1016/j.tibtech.2017.07.004.

[12] A detailed and up-to-date review on the topic of ageing therapies, including a ranking of their predicted effectiveness, can be found in: Partridge, L., Fuentealba, M., & Kennedy, B.K., 2020. The quest to slow ageing through drug discovery. *Nature Reviews Drug Discovery* [e-journal] https://doi.org/10.1038/s41573-020-0067-7 (paywall).

[13] Calorie Restriction is the long-term reduction of calory intake without malnutrition. It has been shown to be a reliable way of extending both life- and health-span in mammals. Importantly, many of the effects seen in monkeys have been mirrored in humans over short timespans. See, Mattison, J., et al. 2017. Caloric restriction improves health and survival of rhesus monkeys. *Nature Communications* [e-journal] https://doi.org/10.1038/ncomms14063 and Redman, L. M., et al., 2018. Metabolic Slowing and Reduced Oxidative Damage with Sustained Caloric Restriction Support the Rate of Living and Oxidative Damage Theories of Aging. *Cell Metab*olism [e-journal] https://doi.org/10.1016/j.cmet.2018.02.019.

[14] Although calorie restriction is a proven way of extending life- and health-span in mammals, maintaining such a diet long-term is difficult. Research into mimicking the effects of calorie restriction using drugs instead of the diet is active. These molecules frequently work on autophagy pathways, a sort of recycling of cellular material pathway. See, Madeo, F., 2019. Caloric Restriction Mimetics against Age-Associated Disease: Targets, Mechanisms, and Therapeutic Potential. *Cell Metabolism* [e-journal] https://doi.org/10.1016/j.cmet.2019.01.018.

[15] The clearance of senescent cells (see Endnote 4) has been shown to have promise in improving certain aspects of ageing-related conditions. Many biotechnology companies are developing drugs to remove these cells from the circulation and from tissues, using a variety of different approaches, including CAR-T cells, monoclonal antibodies – Siwa Therapeutics, traditional small molecule drugs – Unity Biotechnology, and even a DNA based treatment – Oisín Biotechnologies. See, Serrano, M., & Barzilai, N. 2018. Targeting senescence. *Nature Medicine* [e-journal] https://doi.org/10.1038/s41591-018-0141-4 and Gil, J., & Wagner, V., 2020. T cells engineered to target senescence. *Nature* [e-journal] https://doi.org/10.1038/d41586-020-01759-x.

[16] This suggests that it is something present in the blood of old mice that is harmful, rather than the blood of young mice being rejuvenating *per se*. In 2005 researchers demonstrated that, by linking the circulatory systems (parabiosis) of older mice to younger mice, signs of ageing could be reversed in older mice. See, Conboy, I.M., et al., 2005. Rejuvenation of aged progenitor cells by exposure to a young systemic environment. *Nature* [e-journal] https://doi.org/10.1038/nature03260 (paywall). While numerous proteins in the blood were suggested to be involved, including GDF11, VCAM1, and CCL11, no individual factor has yet been demonstrated to be solely responsible in animals or humans. Keen to capitalise on the hype surrounding these findings, at least one company began pay-to-take-part clinical trials in which people had their blood replaced with that of younger donors. The ethics of this are dubious, as is the lack of a control group, which makes assessing the outcome of the treatment difficult. See, Maxmen, A., MIT Technology Review, 2017. *Questionable "Young Blood" Transfusions Offered in U.S. as Anti-Aging Remedy*. Available at: [online] <https://www.technologyreview.com/s/603242/questionable-young-blood-transfusions-offered-in-us-as-anti-aging-remedy> [Accessed 26 October 2020]. Follow-up work demonstrated that it was not the presence of youthful blood that restored the function of the elderly mice's organs, but the dilution of factors present in elderly blood, and that by simply adding a protein-saline solution to the blood of elderly mice, signs of ageing could be reversed. See, Mehdipour, M., et al., 2020. Rejuvenation of three germ layers tissues by exchanging old blood plasma with saline-albumin. *Ageing* [e-journal] https://doi.org/10.18632/aging.103418

[17] A database of drugs with reported effects on extending life- and health- span is maintained by the following research group, which details the organisms in which a compound has demonstrated an effect, and the magnitude of the effect seen. See, Barardo, D., 2017. The DrugAge database of aging-related drugs. *Aging Cell* [e-journal] https://doi.org/10.1111/acel.12585. The evidence for most dietary supplements providing effective life extension in humans is limited. Antioxidants, found in many berries, dark chocolate, and coffee have been demonstrated to have no effect in lowering mortality in a review of studies involving a total of nearly 300,000 participants. See, Bjelakovic, G., et al., 2012. Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. *Cochrane Database of Systematic Reviews* [e-journal] https://doi.org/10.1002/14651858.CD007176.pub2. There is evidence that vitamin D_3 may have a small effect on mortality in adults, warranting further investigation, but no evidence for its improving age-related conditions. See, Bjelakovic, G., et al., 2014. Vitamin D supplementation for prevention of mortality in adults. *Cochrane Database of Systematic Reviews* [e-journal] https://doi.org/10.1002/14651858.CD007470.pub3.

[18] Metformin is an approved drug to treat diabetes, but which appears to target a number of aging-related mechanisms relating to metabolism and growth. In animal experiments metformin has demonstrated the ability to extend life- and health-span. However, these benefits have not yet been detected in humans. Large-scale clinical trials are underway, notably the Targeting Ageing with Metformin (TAME) trial. See, Barzilai, N., 2016. Metformin as a Tool to Target Aging. *Cell Metabolism* [e-journal] https://doi.org/10.1016/j.cmet.2016.05.011 & Soukas, A. A., 2019. Metformin as Anti-Aging Therapy: Is It for Everyone? *Trends in Endocrinology & Metabolism* [e-journal] https://doi.org/10.1016/j.tem.2019.07.015 (paywall).

[19] Rapamycin is a drug approved for the treatment of cancer and post-organ transplant. It has been demonstrated to extend the life- and health- span of several types of animal, including worms, mice, and dogs. It has complex effects on various aspects of ageing, although has also been associated with short-term disruption of metabolism. Further studies are required to understand its disparate effects better. So far, the only human studies have demonstrated its use in improving responsiveness to vaccines in the elderly. See, Kaeberlein, M., & Kennedy, B., 2009. A midlife longevity drug? *Nature* [e-journal] https://doi.org/10.1038/460331a and Mannick, J.B., et al., 2018. TORC1 Inhibition Enhances Immune Function and Reduces Infections in the Elderly. *Science Translational Medicine* [e-journal] https://doi.org/10.1126/scitranslmed.aaq1564.

[20] A molecule fund commonly in the Mediterranean diet, spermidine was originally isolated from human semen, hence the name. It has been associated with a number of molecular pathways common to calorie restriction and improved longevity in animal experiments. Whether these effects are mirrored in humans is yet to be determined. See, Made o, F., 2018. Spermidine in health and disease. *Science* [e-journal] https://doi.org/10.1126/science.aan2788.

[21] Resveratrol has been suggested to extended lifespan, mimicking aspects of calorie restriction. Its presence in red wine was suggested as a potential explanation to the observation that, despite eating a high-fat diet, people in Southern France reported lower rates of heart disease. However, evidence has been less than definite with early animal studies, finding that resveratrol did not prevent obesity but did prevent obesity-associated disease, at least in one strain of mouse, and conferred a nearly normal lifespan on these mice. See, Kaeberlein, M., Rabinovitch, P., 2006. Grapes versus gluttony. *Nature* [e-journal] https://doi.org/10.1038/nature05308. In humans the picture is even more ambiguous, with an assessment of the many clinical trials that have been carried out finding that, while it may decrease some markers of inflammation in the blood, it may not affect others, warranting further research. See, Haghighatdoost, F., & Hariri, M., 2019. Can resveratrol supplement change inflammatory mediators? A systematic review and meta-analysis on randomized clinical trials. *European Journal of Clinical Nutrition* [e-journal] https://doi.org/10.1038/s41430-018-0253-4 (paywall) and Berman, A.Y., et al. 2017. The therapeutic potential of resveratrol: a review of clinical trials. *npj Precision Oncology* [e-journal] https://doi.org/10.1038/s41698-017-0038-6.

[22] Stem cell treatments are at a relatively developed stage of implementation, currently undergoing clinical trials, and having shown some promise. Two small studies evaluating the safety of treating age-related frailty with stem cells obtained from patient's fat tissue showed remarkable improvements in clinical markers such as walking speed and quality of life, and showed no adverse effects. See, Le Couteur, D. G., et al., 2017. Stem Cell Transplantation for Frailty. *The Journals of Gerontology* [e-journal] https://doi.org/10.1093/gerona/glx158. This research is being continued in larger clinical trials run by the company Longeveron. See, Longeveron LLC, 2020. *Phase IIb Trial to Evaluate Longeveron Mesenchymal Stem Cells to Treat Aging* Frailty. Clinicaltrials.gov [online] Available at: <https://clinicaltrials.gov/ct2/show/NCT03169231> [Accessed 26 October 2020]. Other work, currently at an early experimental stage, has demonstrated the possibility of inducing stem cells in patients, using a cocktail of messenger RNAs (mRNAs). This treatment improved a number of age-related process at the molecular level, providing further evidence for the approach. See, Sarkar, T.J., et al., 2020. Transient non-integrative expression of nuclear reprogramming factors promotes multifaceted amelioration of aging in human cells. *Nature Communications*. [e-journal] https://doi.org/10.1038/s41467-020-15174-3.

[23] Although individual genes have been linked to ageing, and demonstrated to have significant effects when mutated, ageing is multi-factorial, involving the interactions of many genes, their products, and the environment. Some estimates place the genetic component as responsible for between 10-30% of the effects seen in ageing. Because of this, it is perhaps unlikely that a single genetic treatment will lead to dramatic improvements in healthy ageing. However, attempts to correct multiple genes

simultaneously have been successful in reversing age-related chronic diseases in animals. See, Noah, D., 2019. A single combination gene therapy treats multiple age-related diseases. *PNAS* [e-journal] https://doi.org/10.1073/pnas.1910073116.

[24] Cryonics has yet been demonstrated to be possible. It is thought that too much damage to the brain's neuronal connections occur during the freezing and thawing processes to enable restoration at a later date. The closest researchers have come is keeping pigs' brains alive (and still ageing) outside of the body for a further 36 hours, following 4 hours without any blood flow. They did not maintain the electrical connections in the brain, the kind of signals associated with higher consciousness. See, Reardon, S., 2019. Pig brains kept alive outside body for hours after death. *Nature* [e-journal] https://doi.org/10.1038/d41586-019-01216-4.

[25] This is true of many pharmaceutical interventions in development, and can perhaps be expected of organisms whose biology differs from that of humans by thousands of years of evolution. Although there are broad similarities in both genetics and molecular pathways, rigorous clinical studies are required in humans before treatments can be deemed to be effective. See, Singh, P.P., 2019. The Genetics of Aging: A Vertebrate Perspective. *Cell* [e-journal] https://doi.org/10.1016/j.cell.2019.02.038, and Perlman, R.L., 2016. Mouse models of human disease: An evolutionary perspective. *Evolution, Medicine, and Public Health* [e-journal] https://doi.org/10.1093/emph/eow014.

[26] Clinical studies usually look to treat a disease, and determine improvement, on the basis of a number of disease-relevant parameters. In the case of cancer this will be, *does the tumour shrink in size?* Given the length of a human life, it would be impossibly expensive to follow enough people through their entire lives to determine whether a given treatment truly extends lifespan. For this reason, it is recognised that surrogate parameters are required, to indicate that the ageing process is slowing or reversing. See,
Kirkland, J.L., 2016. Translating the Science of Aging into Therapeutic Interventions. *Cold Spring Harbour Perspectives in Medicine* [e-journal] https://doi.org/10.1101/cshperspect.a025908.

[27] These surrogate endpoints would have to demonstrate to regulatory agencies that they accurately reflect lifespan, and could be tests of muscle strength or circulating markers of inflammation. Another option is to look at epigenetic markers of age that strongly correlate with chronological age. See, Jylhävä, J., Pedersen, N.L., & Hägg, S., 2017. Biological Age Predictors. *EBioMedicine* [e-journal] https://doi.org/10.1016/j.ebiom.2017.03.046 and Lu, A.T., et al., 2019. DNA Methylation GrimAge Strongly Predicts Lifespan and Healthspan. *Aging* [e-journal] https://doi.org/10.18632/aging.101684.

[28] Clinical testing based on ageing itself as an indication is now permitted by the U.S. Federal Drug Administration (FDA), and the 2018 version of the WHO's International Classification of Diseases (ICD-11) included for the first time an extension code "Ageing-Related" (XT9T) for ageing-related diseases, thereby recognising ageing as a major risk factor. See, Fleming, G.A., et al., 2019. A Regulatory Pathway for Medicines That Target Aging. *Public Policy & Aging Report* [e-journal] https://doi.org/10.1093/ppar/prz018 (paywall) and, World Health Organization, 2019. *ICD-11 for Mortality and Morbidity Statistics*. WHO [online] Available at: <https://icd.who.int/browse11/l-m/en#/http://id.who.int/icd/entity/459275392> [Accessed 26 October 2020].

[29] One promising early intervention in ageing was that of lengthening telomeres, the DNA caps on the chromosomes of human genomes (see Endnote 5). This is a naturally occurring process but, as we age, it diminishes and the telomeres shorten. Despite this impressive correlation it was found that artificially extending the telomeres by increasing the amount of protein responsible for this process did extend lifespan, it also increased the risk of developing cancer. This was because those pre-cancerous cells that would otherwise be terminated were kept alive. See, Kuo, C-L., et al., 2019. Telomere length and aging-related outcomes in humans: A Mendelian randomization study in 261,000 older participants. *Aging Cell* [e-journal] https://doi.org/10.1111/acel.13017.

[30] Getting older is the biggest risk for developing a chronic disease (such as diabetes, cardiovascular disease, neurodegenerative disease, chronic kidney disease, or cancer) and in developed countries accounts for large proportion of healthcare expenditure. Given the expected increase in the proportion of elderly in the world, addressing the associated expected increase in chronic health disease by extending health-span could reduce much of the pain associated with shifting demographics, notwithstanding issues of social welfare and workforce participation. See, Kennedy, B.K., et al., 2014. Aging: a common driver of chronic diseases and a target for novel interventions. *Cell* [e-journal] Available at: https://doi.org/10.1016/j.cell.2014.10.039, Goldman, D., 2013. Substantial Health and Economic Returns From Delayed Aging May Warrant a New Focus for Medical Research. *Health Affairs* [e-journal] Available at: https://doi.org/10.1377/hlthaff.2013.0052, and Llewellyn, J., & Chaix-Viros, C., 2008. *The Business of Ageing*, Nomura [online] Available at: <https://www.nomura.com/resources/europe/pdfs/TheBusinessOfAgeing.pdf> [Accessed 26 October 2020].