



## Dublin Longevity Declaration

### Consensus Recommendation to Immediately Expand Research on Extending Healthy Human Lifespans

For millennia, the consensus of the general public has been that aging is inevitable. For most of our history, even getting to old age was a significant accomplishment – and while centenarians have been around at least since the time of the Greeks, aging was never of major interest to medicine.

That has changed. ***Longevity medicine has entered the mainstream.*** First, evidence accumulated that lifestyle modifications prevent chronic diseases of aging and extend healthspan, the healthy and highly functional period of life. More recently, longevity research has made great progress – aging has been found to be malleable and hundreds of interventional strategies have been identified that extend lifespan and healthspan in animal models. Human clinical studies are underway, and already early results suggest that the biological age of an individual is modifiable.

A concerted effort has been made in the longevity field to institutionalize the word “healthspan”. Why healthspan (how long we stay healthy) and not its side-effect of lifespan (how long we live)? The reasons are linked more to perception than reality. Fundamental to this need to highlight healthspan is the idea that individuals get when they are asked if they want to live longer. Many imagine their parents or grandparents at the end of their lives when they often have major health issues and low quality of life. Then they conclude that they would not choose to live longer in that condition. This is counter to longevity research findings, which show that it is possible to intervene in late middle life and extend both healthspan and lifespan simultaneously. Emphasizing healthspan also reduces concerns of some individuals about whether it is ethical to live longer.

A drawback of this exists, though: many current longevity interventions may extend healthspan more than lifespan. Lifestyle interventions such as exercise probably fit this mold. Many interventions that have dramatic health-extending effects in invertebrate models have more modest effects in mice, and there is a concern that they will be further reduced in humans. In other words, the drugs and small molecules that we are excited about today may, despite their hefty development costs and lengthy approval processes, only extend average healthspan by five or ten years and may not extend maximum lifespan at all. Make no mistake, this would still represent a revolution in medical practice!

***A five-year extension in human healthspan, with equitable access for all people, would save trillions per year in healthcare costs, provide extra life quality across the entire population and***

**ameliorate the demographic challenges that are happening in the first half of this century.** Most experts in the field now acknowledge that this is a likely outcome in the near future and one focus of longevity medicine is now on achieving it. But far more is possible.

Arguably, the avoidance of an emphasis on lifespan is a consequence of an overly pragmatic approach to two fundamental questions: **Why do humans age and what can we do about it?** These are surely two of the biggest questions in human biology. Although we try our best to ignore it, the prospect of an inevitable decline in health leading to mortality shapes our thoughts and actions. Despite the incredible advances in longevity research, these questions remain unanswered. What biological processes bring about the aged state? Can aging not just be significantly slowed, but more and more thoroughly reversed? How would humans, and their societies, be different if we achieve these goals? It will cost billions of dollars in research and significant time to answer such questions, but we assert that it would undoubtedly pay for itself many times over. The case can (and will) be made that these questions should be answered because the knowledge gained will inevitably lead to major medical advances. Another reason is the one that is not utility-driven, but rather the classic “knowledge for knowledge’s sake” argument. Understanding ourselves and the organisms around us used to be reason alone to do research, and answering basic questions reliably yields utility in the future. Penicillin comes to mind! But the quest for knowledge, especially on ubiquitous topics such as aging, is worthy in its own right.

Achieving much better control of aging would not mean immortality, of course. Nevertheless, it would dramatically change the world we live in and how we live in it. Life quality may expand, fear of loss of independence may diminish and, over time, the fabric of our world may radically improve. What would it mean? Imagine the energy of youth combined with the wisdom of experience. Think about living long enough for space travel. Imagine going back to school at 80 to study the latest in scientific breakthroughs, starting a new career, seeing your great-great-grandkids. Yes, there will be unexpected outcomes and some might raise new challenges — but the same was true of past technological advances that few of us would give back. How many of us want to go back in time now? How many will want to in the future? **Optimism about a better future drives us still, and one way to move forward is to answer the big questions in biology. The grand challenge of aging is foremost among these.**

What cards need to be turned over to answer the longevity question? What interventional strategies are likely to take us beyond modest healthspan effects and toward radical change in the rate of biological aging? — beyond rough knowledge of the biology underlying aging toward true understanding?

Biogerontological research is often reductionist in nature, drilling down to the pathways, proteins and genes that influence how we age. This has been successful, but it is now evident that the processes that control aging represent an inter-linked network of interactions that eventually cause the aged phenotype to emerge at the whole-organism level. A new systemic thinking is needed to solve the “why we age” question. Strategies need to be employed to reconstruct the molecular alterations and pathways and integrate them into a unified model that explains aging. Such a synthesis requires a multi-disciplinary approach combining methods and tools from molecular biology, complex systems theory, and the physical and engineering sciences. It can be greatly facilitated by the growing availability of human biomedical data, such as Electronic Medical Records. AI-driven modeling is making progress in this arena, leading to measures of biological age, new interventions and understanding of the relative contributions of different aspects of aging. However, it is important to move beyond black-box modelling to obtain meaningful models of the aging process which can **not only describe, but also explain that process in terms that are understandable and actionable.**

Most of the lifestyle or small-molecule interventions that are currently being tested target pathways affecting longevity. These include those designed to improve metabolism, restore youthful immune function, maintain youthful body composition, eliminate deleterious cells or improve cellular stress responses. But there are strategies on (and just over) the horizon that may have much bigger impact. These need to be seriously interrogated and resources need to be devoted to these big questions. There needs to be an acceptance and tolerance of significantly higher levels of failure in longevity research, knowing that big ideas are sometimes wrong and that the ones that are right will far outweigh the setbacks.

Below, we list some of the promising interventional ideas on the horizon and speculate on what is not yet visible. ***These (and other) examples should be the basis for discussion by a taskforce designed to re-invigorate the concept of achieving control over our most inevitable biological outcome – age-related morbidity and mortality.***

Some Emerging Strategies and Questions:

- ***Combinatorial approaches*** – Can multiple systems be targeted simultaneously and will that yield synergistic outcomes?
- ***Novel classes of small molecules*** – We have only explored a narrow subset of the small-molecule space for longevity outcomes. Will larger-scale screens or even novel screening approaches result in enhanced lifespan extension?
- ***Cellular Reprogramming*** – Can we reprogram somatic cells in our tissues to a state to promote replacement of damaged cells and restoration of youthful tissue function?
- ***Approaches based on species longevity*** – Can we utilize adaptations of long-lived species to achieve human longevity comparable to nature’s greatest successes, exceeding the modest changes delivered by existing interventions?
- ***Gene and Cell Therapy*** – Long promised, both gene therapy and cell therapy have become feasible. Can they be employed to target aging or age-related conditions?
- ***Novel targets*** – for example, gene therapies derived from multi-omics studies. Can they delay or reverse aging processes?
- ***Emerging strategies to reverse age-related deterioration of the epigenome*** – There is good evidence that this deterioration reduces our control of endogenous parasites such as retrotransposons and retroviruses and increases age-related inflammation. Can it be repaired?
- ***Personalizing aging interventions*** – While general events are likely to drive aging, their relative impacts in each individual are likely to vary, therefore understanding how to optimize interventions to the individual will likely have higher yields.
- ***Over the Horizon*** – Often regarded as science fiction, strategies such as cryopreservation, brain mapping and *ex vivo* organ generation may ultimately be feasible. We should keep open the possibility that dramatic lifespan extension may involve technologies that we haven’t fully imagined yet.

Is radical lifespan extension foreseeable? No one can answer that question with certainty. But there are certainly enough tantalizing clues suggesting that aging is sufficiently malleable to warrant the allocation of very substantial resources. ***Imagine a world where we control aging – possibly the biggest breakthrough yet in the ever-changing human condition.***

Visit the Declaration’s web site at <https://dublinlongevitydeclaration.org> to view the list of signatories, and to add your name!