CLUB VITA and Nationwide

# THE RISK OF **LIVING LONGER**

Thank you for joining us – the webinar will start shortly

Douglas and Uli ask the ultimate question of human longevity for financial institutions:

*How long can we go?*

## Season 2 program

| | | | |
|---|---|---|---|
| Session 1<br>Sept 10th, 2024 | *Longevity Science*<br>*– Advancing from Cure to Prevention* | • Dominik Thor,<br>Geneva College of Longevity Science | Recording available here |
| **Session 2**<br>**Oct 22, 2024** | ***Quantifying the effects of gero-science*** | • **Chris Martin & Nicky Draper**<br>**Crystallise** | **Today!** |
| Session 3<br>Nov 14th, 2024 | *Behavio(u)ral change* | • Francois Millard (Vitality)<br>• Tina Woods (Business for Health) | Nov 14th, 2024 |
| Session 4<br>Dec 3rd, 2024 | *Preventing dementia* | • Baroness Professor Susan Greenfield<br>Neuro-Bio Ltd | Dec 3rd, 2024 |

For full details and registration for the series,
visit: www.clubvita.net/us/events or follow http://linkedin.com/company/club-vita

Watch the replays of season 1 here: www.clubvita.net/us/events/event-recording

# THE RISK OF **LIVING LONGER**

*Longevity Science – Quantifying the effects of gero-science*

Douglas Anderson
**(Chair)**
Club Vita

Ulrich Stengele
**(Chair)**
Nationwide Financial

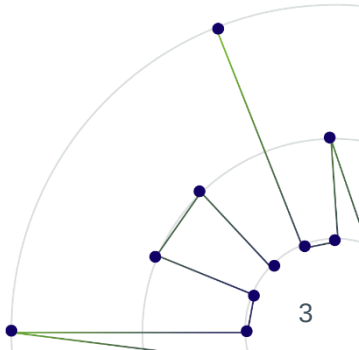
Chris Martin
**(Panelist)**
Crystallise Ltd

**Nicky Draper**
**(Panelist)**
Crystallise Ltd

# Poll question

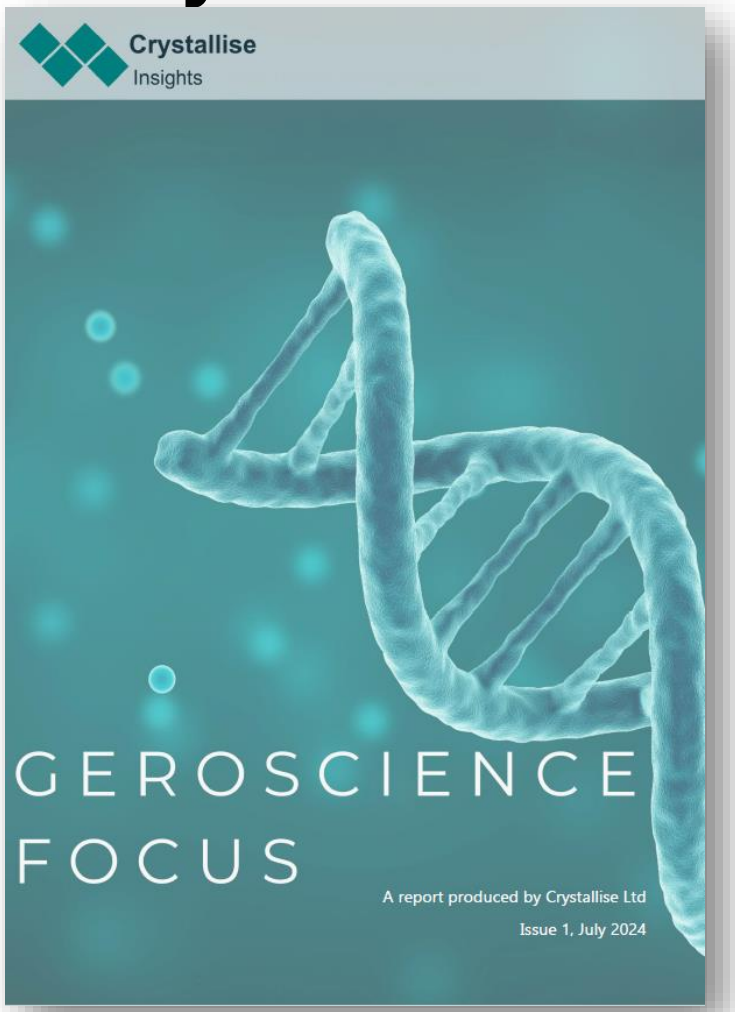
*“How familiar are you with the concept of gero-therapeutics?”*

- *Never heard of them*
- *I’ve heard of them, but I’m not entirely sure what they are*
- *I think I have a good understanding of the concept*
- *I am an expert in gero-science and gero-therapeutics*



# Introduction to *gero-science focus* series

# Crystallise Insights: Geroscience Focus




www.crystallise.com

## In-depth reports on Geroscience and Gero-therapeutics

- 2 short form evidence-based articles
- 1 deep dive article modelling the impact of a gero-therapeutic

Produced quarterly by multi-disciplinary team at Crystallise.

# Hallmarks of Ageing


**Primary**
- Telomere shortening
- Epigenetic alterations
- Loss of proteostasis
- Disabled macro-autophagy
- Genomic instability

**Antagonistic**
- Mitochondrial dysfunction
- Cellular senescence
- Deregulated nutrient-sensing

**Integrative**
- Chronic inflammation
- Altered intercellular communication
- Dysbiosis
- Stem cell exhaustion

# Description of the framework and modelling approach

# Effect size in mice - longevity

- Meta-analysis of **18 trials** of **rapamycin** on the lifespan of mice. Average of a **12% increase in lifespan** across the studies.
- **15 trials** with sufficient data to estimate the effect on the **rate of aging itself**.
- Fitting mortality models to the data suggest the **rate of aging** is reduced by about **39%**.

Image generated by ChatGPT, August 23, 2024, OpenAI

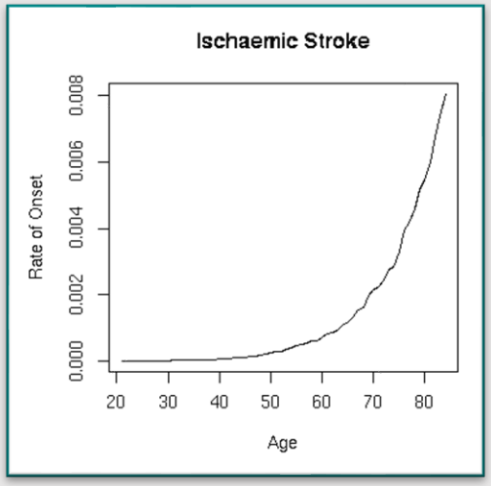


Mannick JB, Lamming DW. Targeting the biology of aging with mTOR inhibitors. Nat Aging. 2023;3:642–60.

# Modelling effect in humans – diseases and aging

*Kuan, V., Fraser, H.C., Hingorani, M. et al. Data-driven identification of ageing-related diseases from electronic health records. Sci Rep 11, 2938 (2021). https://doi.org/10.1038/s41598-021-82459-y*

Mined 3 million patient health records for **age of onset** of high-burden diseases.




Fit to a **Gompertz-Makeham (GM) model**

We use **goodness of fit** ($R^2$) as a proxy measure of aging-relatedness of the disease – **"How much might progression of this disease be amenable to gerotherapeutics?"**

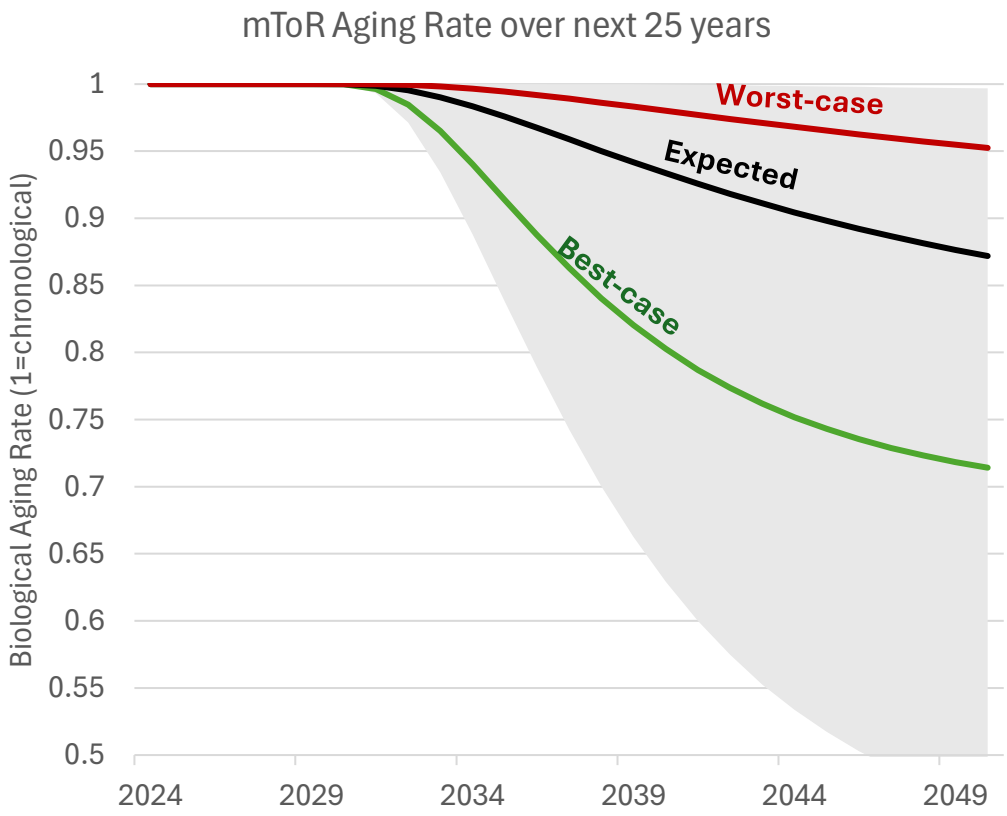
# Overall Results – Real-World Scenarios

General Population

**mTOR with 37%** reduction in aging-rate

Fast (Best), Typical, Slow (Worst) time to market

Excellent (Best), Typical, Poor (Worst) Access / Compliance



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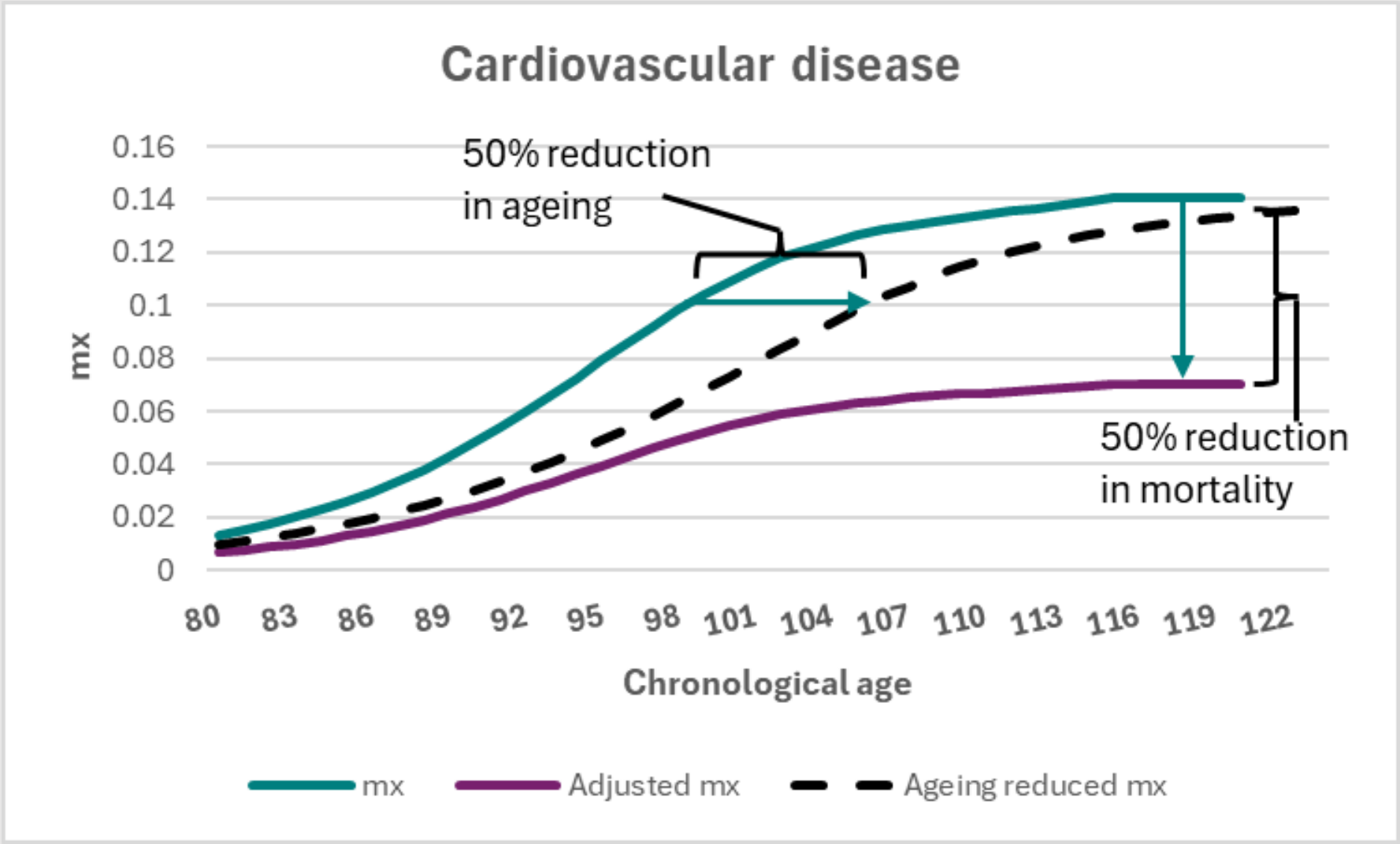
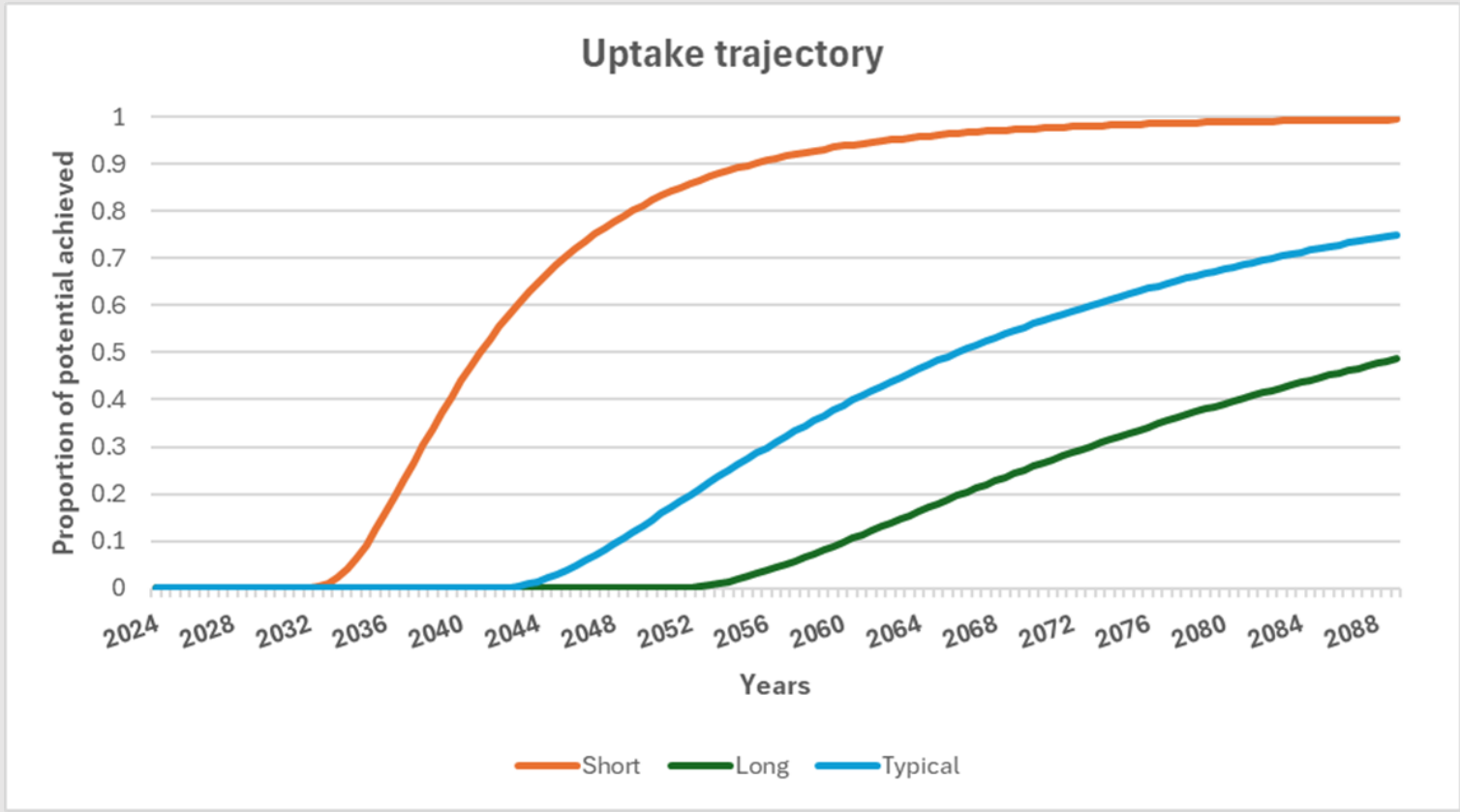
# Modelling ageing versus cause of death

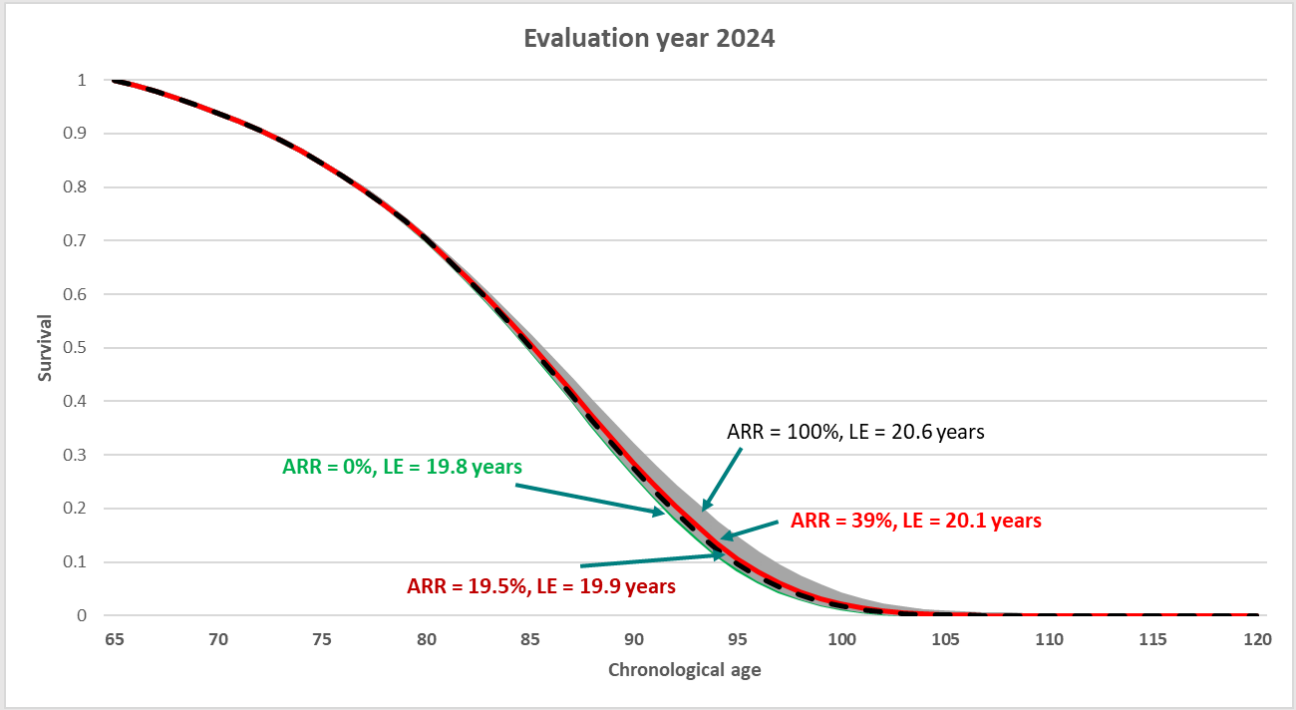


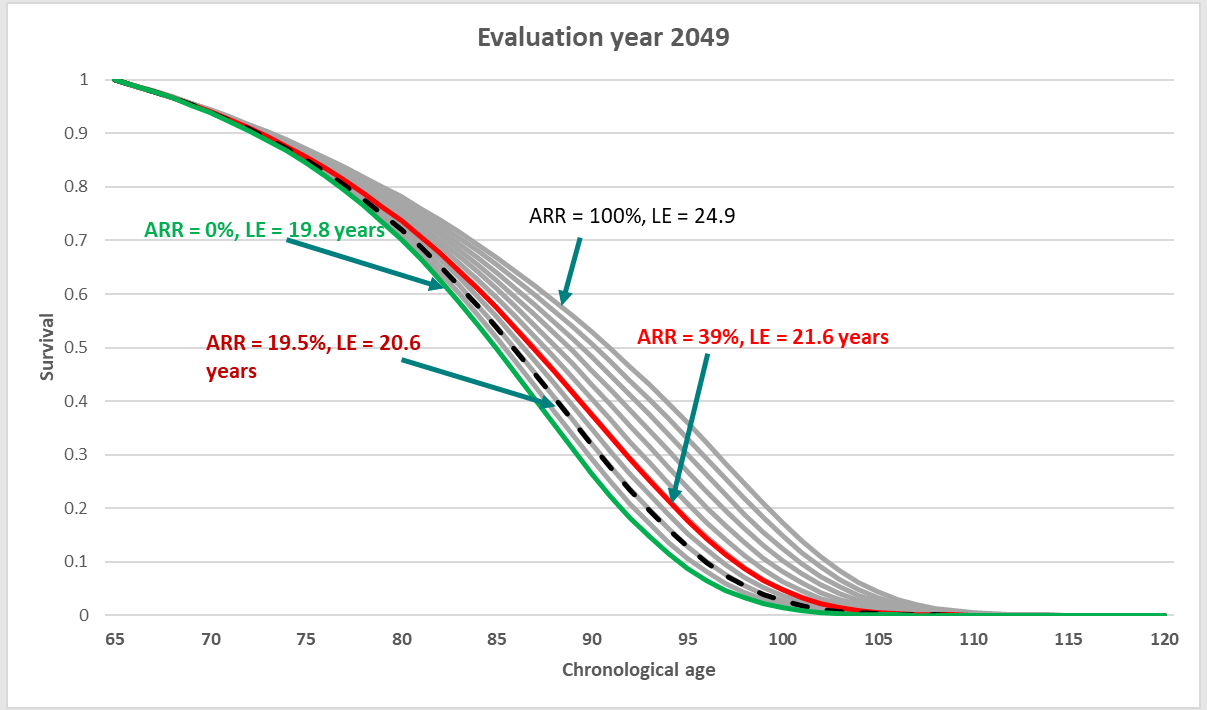
# Uptake trajectories

| | Short | Long | Typical |
|---|---|---|---|
| Pre-clinical | 3 | 6 | 4.5 |
| Phase 1 trials | 0.5 | 4.1 | 2.3 |
| Phase 2 trials | 1 | 6.2 | 3.6 |
| Phase 3 trials | 1 | 5.6 | 3.3 |
| Time to licensing | 0.5 | 2.1 | 1.3 |
| Time to HTA approval | 0.5 | 2 | 1.25 |
| | Years | | |



# Survival of 65-year old man in 2024 and 2049



# Application to specific gero-therapeutic: mTOR inhibitors

# mTOR

| mTOR, an ancient protein switch, triggers growth and is conserved across all animals | When food is abundant, mTOR triggers cells to grow, multiply, and produce more proteins, fats, and cholesterol | Inhibiting mTOR slows cell growth but boosts recycling, clearing out dysfunction and enhancing cell efficiency |
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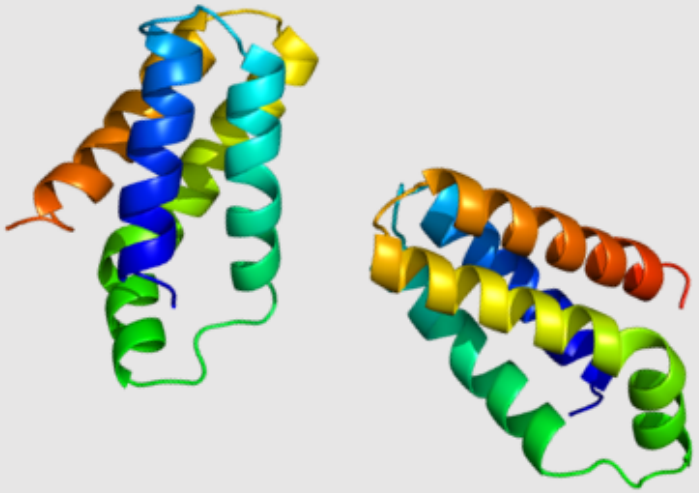
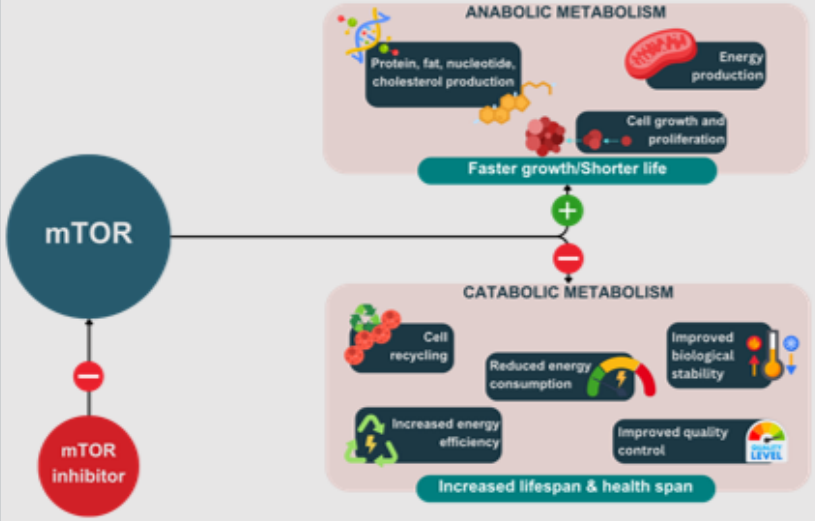
|  |  |   |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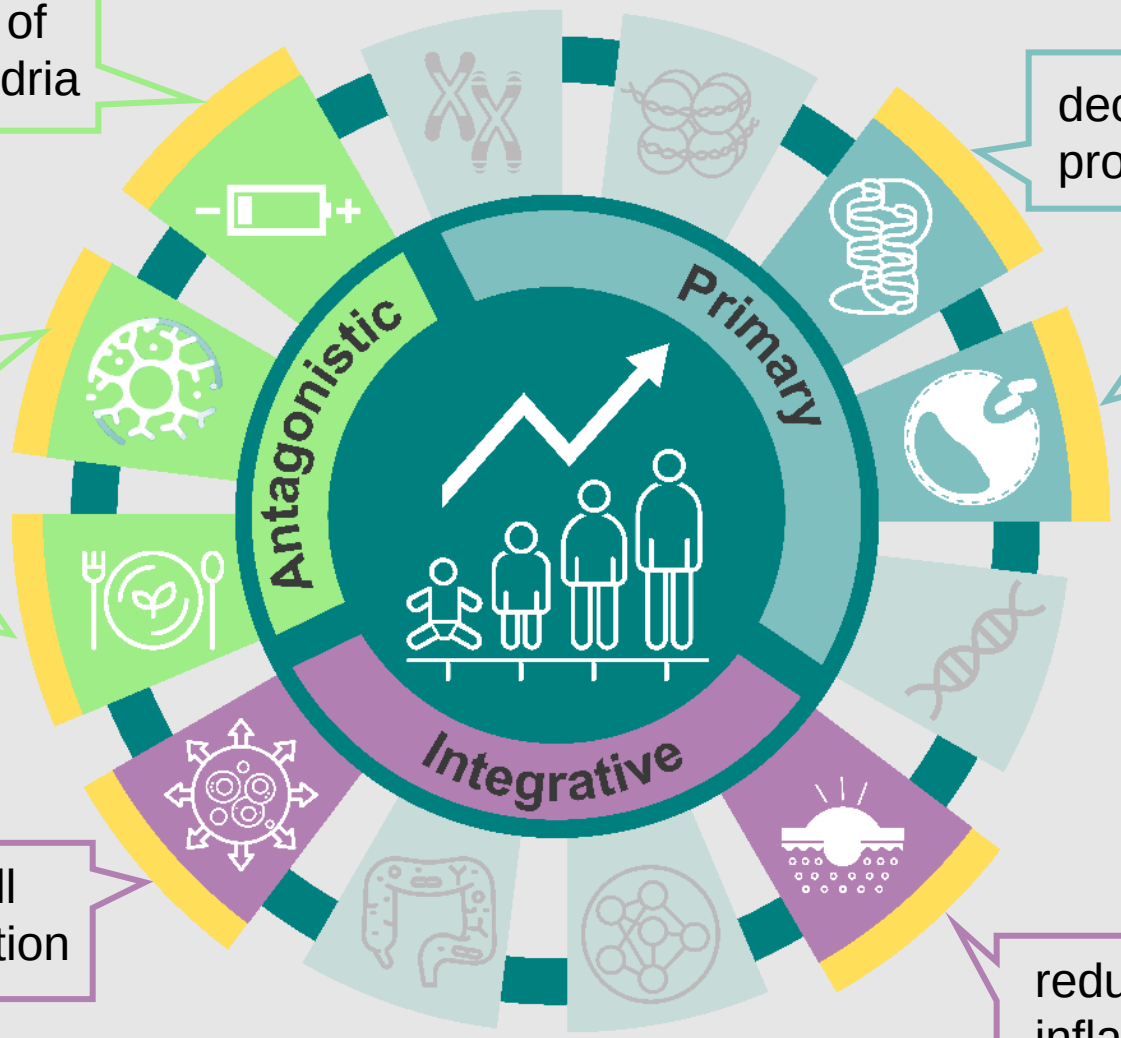
# mTOR inhibition and hallmarks of aging

promotes recycling of inefficient mitochondria

slows down the development of senescent cells

pushes metabolic function to reduced energy consumption and greater energy efficiency

increases stem cell numbers and function



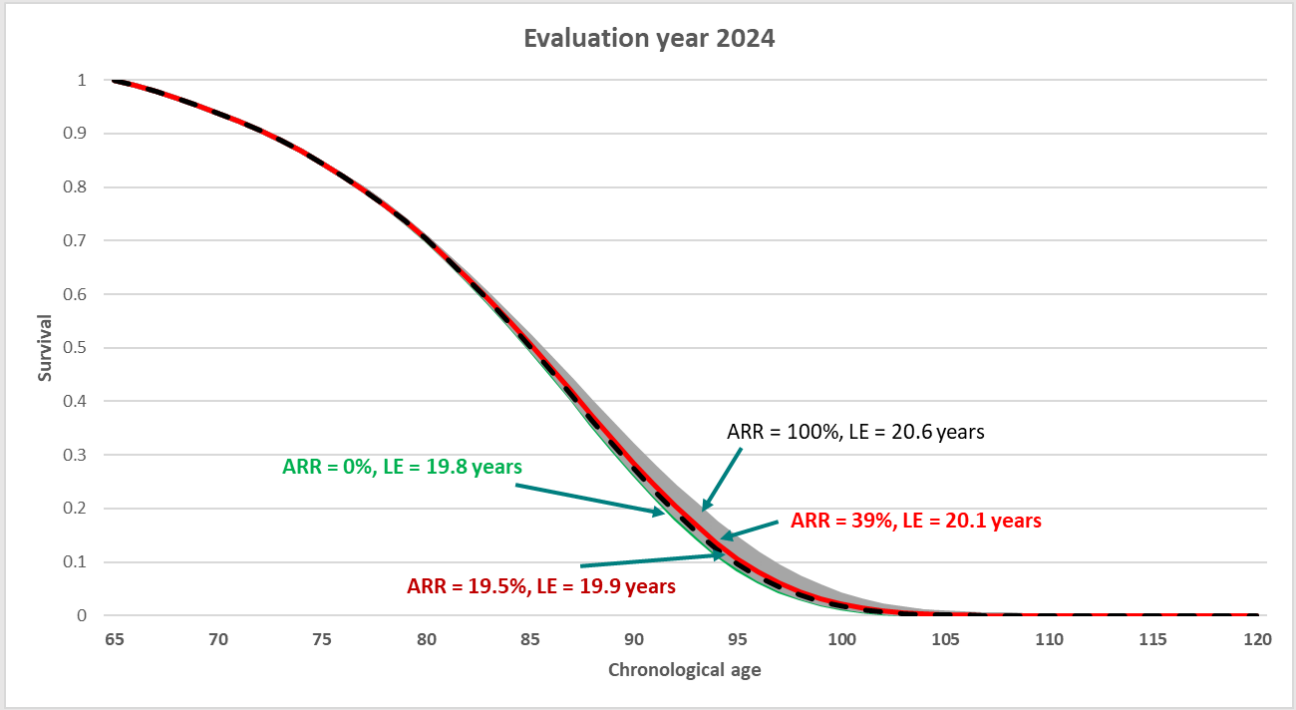

decreases protein production

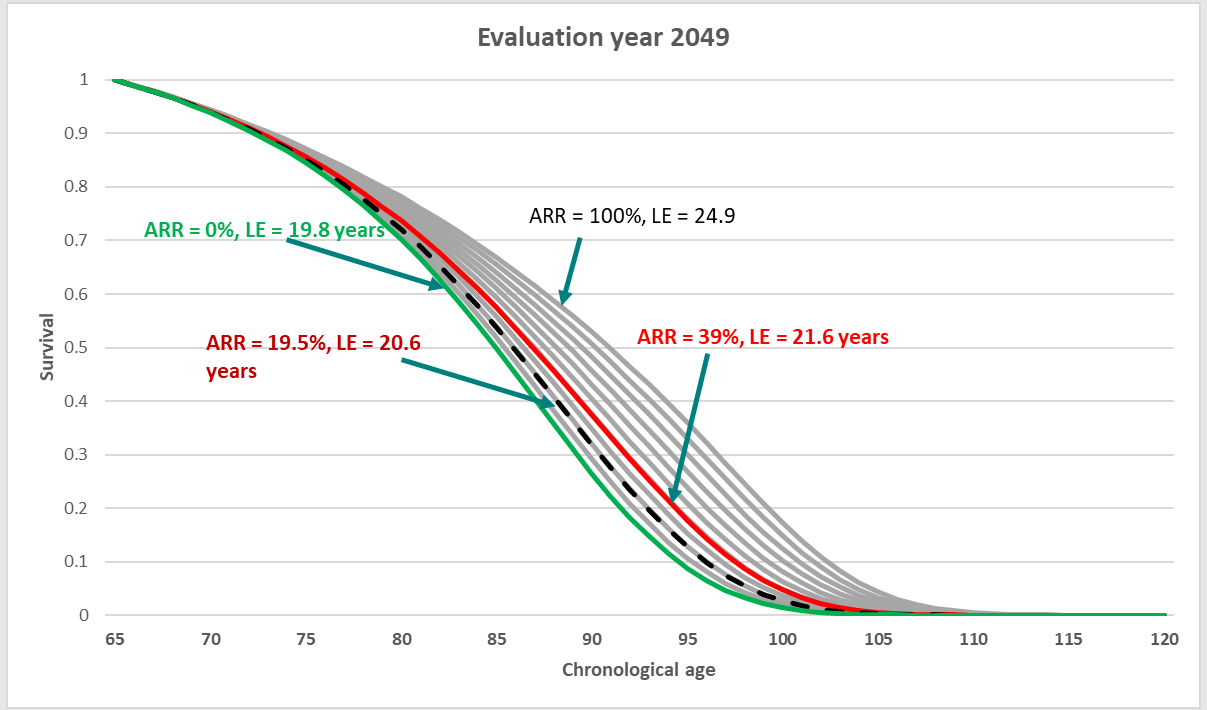
Cell recycling is increased

reduces chronic inflammation

# mTOR inhibitors results

65 year-old man who starts treatment at age 50, if it is available, with a typical trajectory of uptake and typical access and compliance.




ARR assumption of 39% (red) from mouse studies, and reduced 50% to 19.5%(dashed) for longer lifespan of humans. ARR assumptions from 0% to 100% in steps of 10% in grey for comparison.

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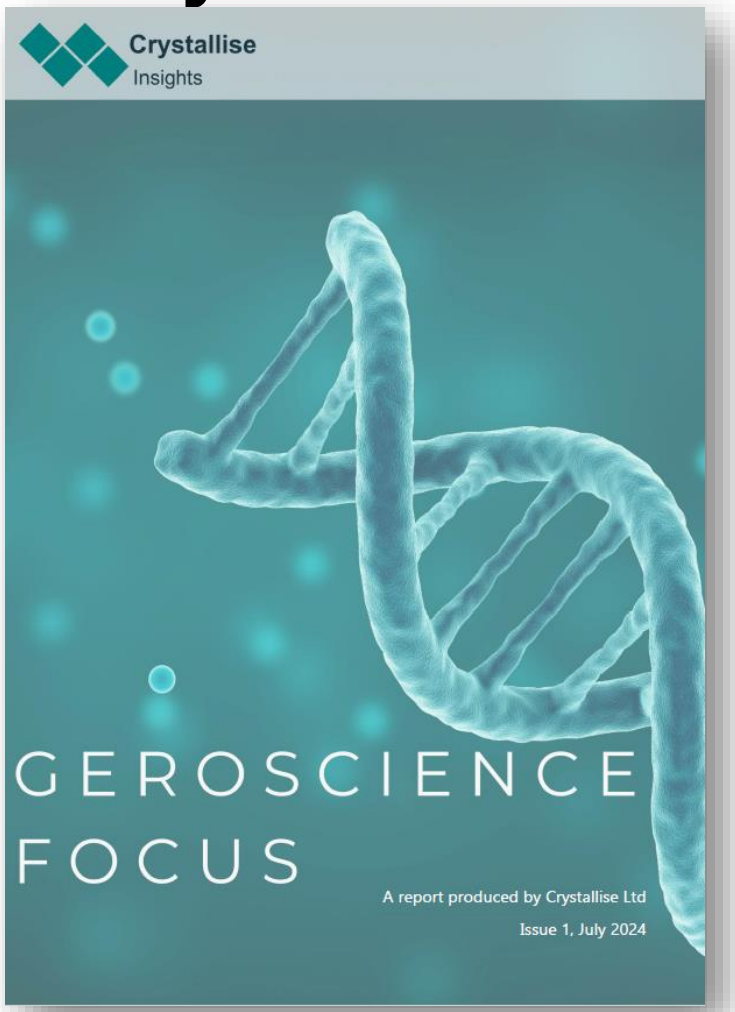


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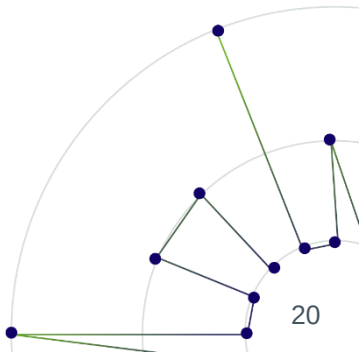
# Poll question

*“On a scale of*
*1 (not for me) to 5 (fantastic)*
*how would you rate today’s webinar?”*



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# Thank you

# Appendix – Hallmarks of Aging

**Telomere shortening** - At the ends of your chromosomes are telomeres, like the protective plastic tips at the ends of shoelaces. Every time a cell divides, these telomeres get shorter. Eventually, they become so short that they can no longer protect the chromosomes, leaving them exposed to damage and increasing the risk of mutations. This process contributes to aging and ultimately leads to cell death when the telomeres are too short to safeguard the chromosomes.

**Epigenetic alterations** - Epigenetics involves changes in how our genes are expressed without altering the underlying DNA sequence. It's like a set of switches that can turn genes on or off, influenced by environmental factors like diet, stress, and exposure to toxins. Over time, these epigenetic changes can accumulate, affecting gene expression in ways that contribute to aging and disease by disrupting the normal functioning of cells.

**Loss of proteostasis** - Proteins are the building blocks of the body, crucial for both structure and function. Once a gene's instructions are used to create a protein, that protein must fold into the right shape to work properly. With age, the body's ability to maintain the correct folding of proteins, called proteostasis, deteriorates. Misfolded or damaged proteins can accumulate and lead to diseases like Alzheimer's, where protein aggregates such as amyloid plaques disrupt normal brain function.

# Appendix – Hallmarks of Aging

**Disabled macro-autophagy** - often shortened to autophagy, is the body's recycling system. It’s a process where cells break down and remove damaged components, recycling parts to maintain cellular health. When this process becomes impaired with age, waste and damaged materials accumulate inside cells, contributing to their dysfunction and accelerating the aging process. It's like a waste disposal system breaking down, leaving garbage to pile up.

**Genomic instability** -Imagine your body's DNA as an instruction manual. Over time, this manual accumulates errors or damage, leading to genomic instability. These errors, or mutations, can disrupt the normal function of cells, leading to diseases like cancer or contributing to aging. Damage to the DNA is not only harmful to the current cell but also gets passed along during cell division, perpetuating the problem in new cells.

**Mitochondrial dysfunction** - Mitochondria are the energy-producing powerhouses of the cell, but with age, they become less efficient. This decline, known as mitochondrial dysfunction, means cells don’t generate as much energy and instead produce harmful by-products like reactive oxygen species (ROS). These toxic molecules damage proteins, lipids, and DNA, further accelerating aging and cell damage—like having faulty, leaky batteries that can’t hold a charge.

# Appendix – Hallmarks of Aging

**Cellular senescence** - is when cells stop dividing in response to stress or damage. Initially, this process is protective, acting as a brake to prevent damaged cells from multiplying and potentially becoming cancerous. However, over time, these senescent cells accumulate, especially when the body's ability to clear them declines. They secrete inflammatory molecules that disrupt tissue repair and promote chronic inflammation, contributing to aging and age-related diseases.

**Deregulated nutrient-sensing** - Our cells have intricate systems to sense and respond to nutrients like glucose and amino acids, ensuring that cells grow and function properly. But with age, this system, including pathways like mTOR and insulin signalling, becomes less responsive, known as deregulated nutrient sensing. This malfunction can lead to excessive cell growth, reduced recycling of cellular components, and chronic inflammation—ultimately contributing to obesity, diabetes, and aging.

**Chronic inflammation** - Inflammation is essential for fighting infections and healing injuries, but as we age, chronic inflammation, sometimes called inflammaging, becomes a problem. Senescent cells secrete molecules that promote inflammation, even when there's no threat or injury. This constant, low-level inflammation damages tissues over time, contributing to diseases like arthritis, heart disease, and Alzheimer's.