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Longevity black swans:

Looking beyond past trends to what potential disruptive developments in medicine, healthcare, technology and lifestyle may mean for life expectancy

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Agenda

- **Introduction: What is a longevity Black Swan?**

- Drivers of longevity extension
  - Lifestyle impact
  - Heath environment impact
  - Medicine impact
  - The facilitating role of technology

- A realistic disruptive scenario

What is a “black swan”?[1]

A Black Swan is

an event or occurrence that deviates significantly beyond what is normally expected and that would be extremely difficult to predict

Characteristics:

- A low-probability outlier, beyond experience and expectation
- It has an extreme impact
- It is explainable afterwards, despite being difficult to predict

1. Nassim Nicholas Taleb, "The Black Swan: The Impact of the Highly Improbable."

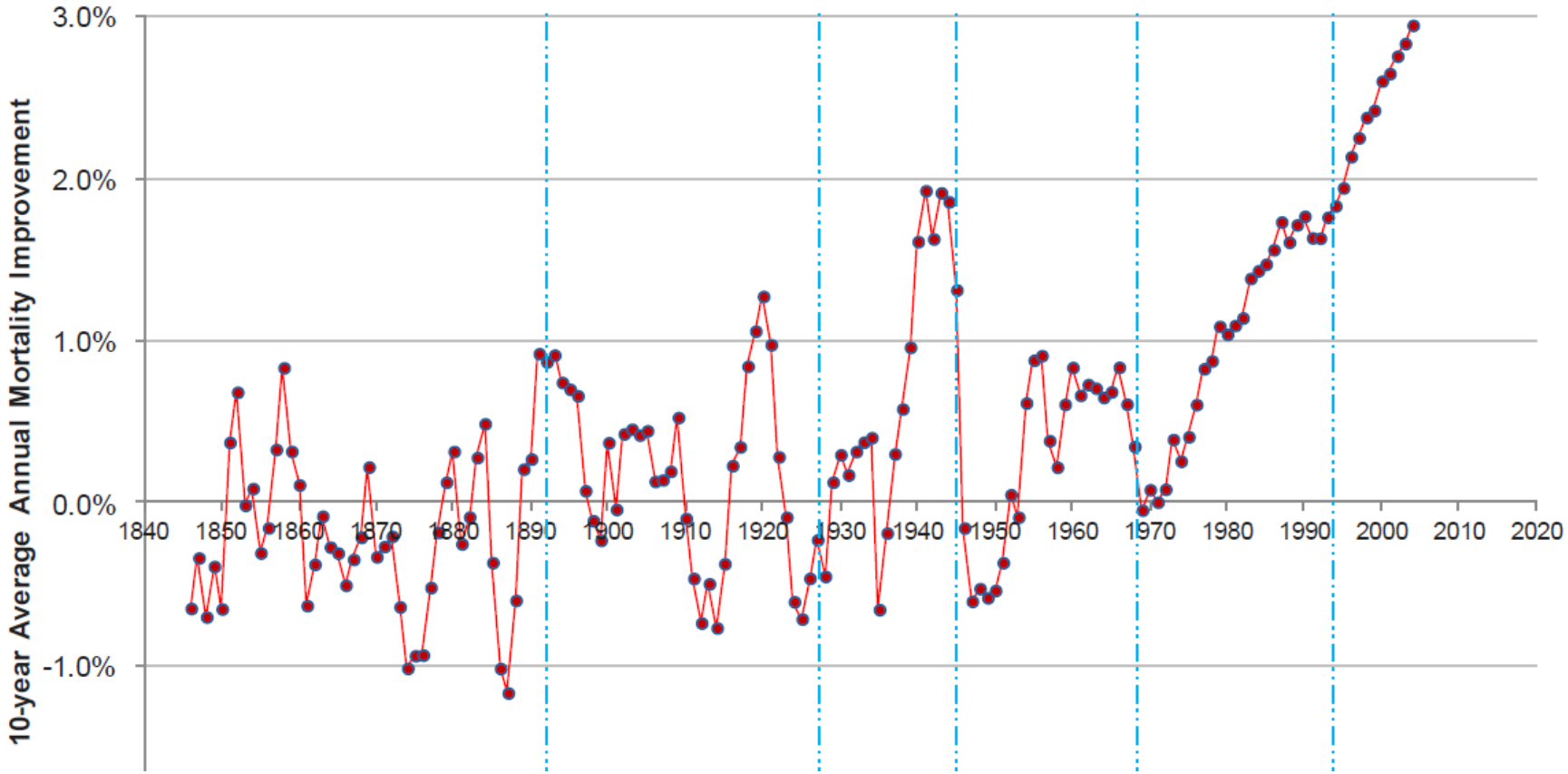
Key question is a question of *risk*

Is there potential for significant extension of human lifespans?

There are potentially enormous financial, social, political implications

Do past mortality improvements suggest a black swan?

Mortality improvement rates for UK males aged 75-85[1]



Source: RMS (2012). "Longevity Risk: Setting the long-term mortality improvement rate. What medical science tells us about future longevity risk"

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Is there scope for a future longevity black swan?

Possible black swans include:

- Closure of the LE gap between different socio-economic classes?
- Closure of the LE gap between countries?
- Increases in overall LE driven by advances in lifestyle, health provision and medicine?

Potential drivers likely to include "disruptors" related to:

- Government policy (health, social, economic)
- Education
- Affluence
- Medical science
- Big data
- Technology

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- A realistic disruptive scenario

There are three well-established categories for the drivers of gains in life expectancy

Lifestyle	Health Environment	Medicine

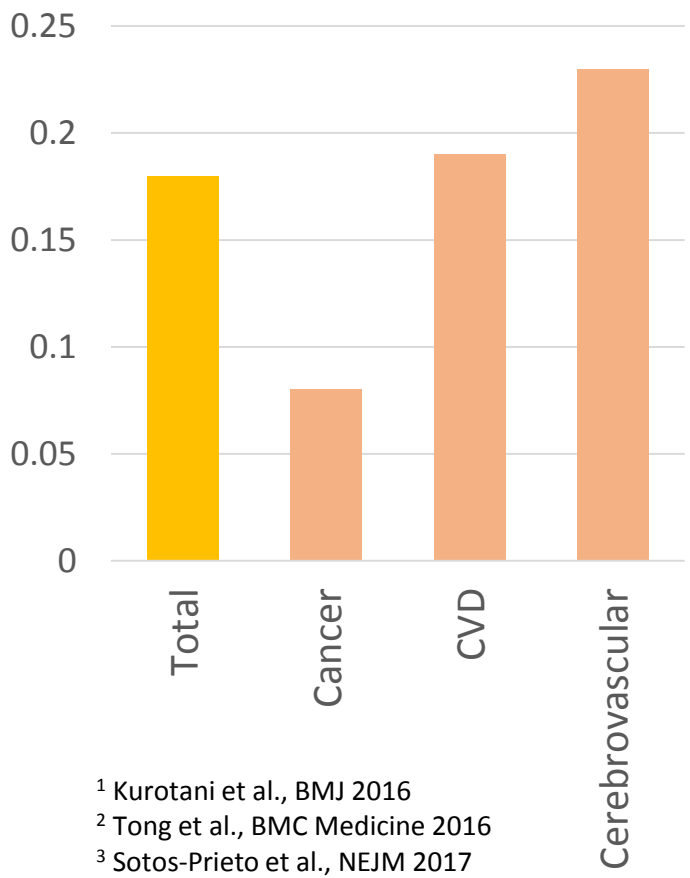
• Diet
• Exercise
• Smoking
• Health-consciousness
	• Healthcare provision
	• Public health
	• Social support
	• Housing & sanitation
	• Pollution
		• Treatments:
		  • CVD
		  • Cancer
		  • Respiratory
		  • Dementia
		• Future developments:
		  • Regenerative medicine
		  • Anti-ageing

These are the obvious starting point for black-swan hunting

Lifestyle: Diet

Japanese diet	**Japan:** BMJ 2016 Size: 79,594
Mediterranean diet	**US:** NEJM, 2017 Size: 73,739
Mediterranean diet	**UK:** BMC Medicine 2016 Size: 23,902

Reduction in mortality hazard rate for high-quality Japanese diet[1]



[1] Kurotani et al., BMJ 2016
[2] Tong et al., BMC Medicine 2016
[3] Sotos-Prieto et al., NEJM 2017

The right diet significantly reduces mortality rates

Lifestyle: Physical exercise

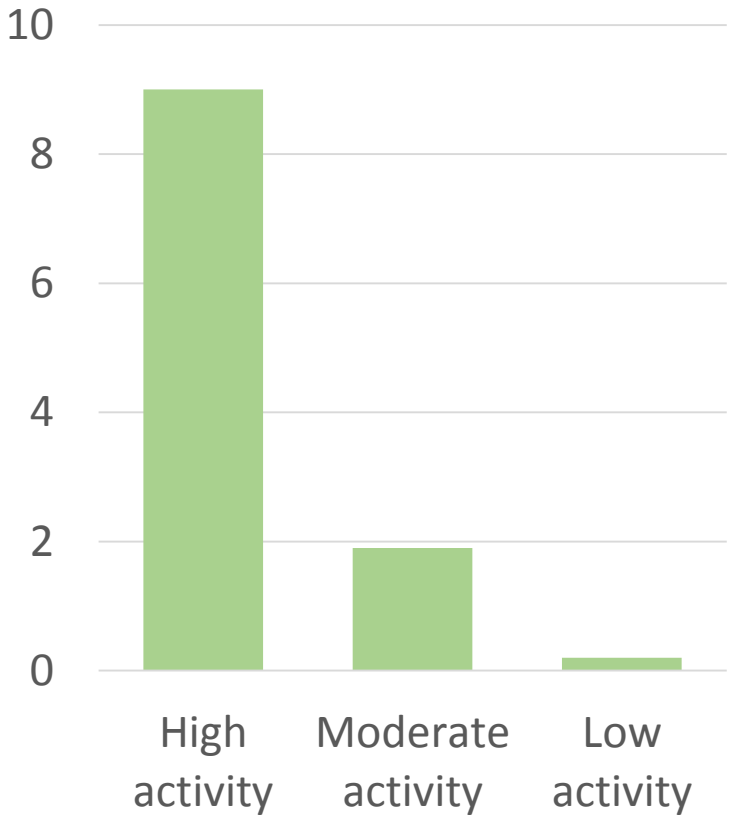
Study of 5823 adults (2017) [1]

- Intense physical exercise
  - Reduces cellular ageing by 9 years
  - Lengthens telomeres
- "High activity" means
  - Jogging 200 minutes per week

Other 2017 studies

- High-Intensity Interval Training improves decline in muscle mitochondria [2]
- Running increases LE by 3 years [3]

Biological ageing advantage (years) relative to sedentary adults[1]

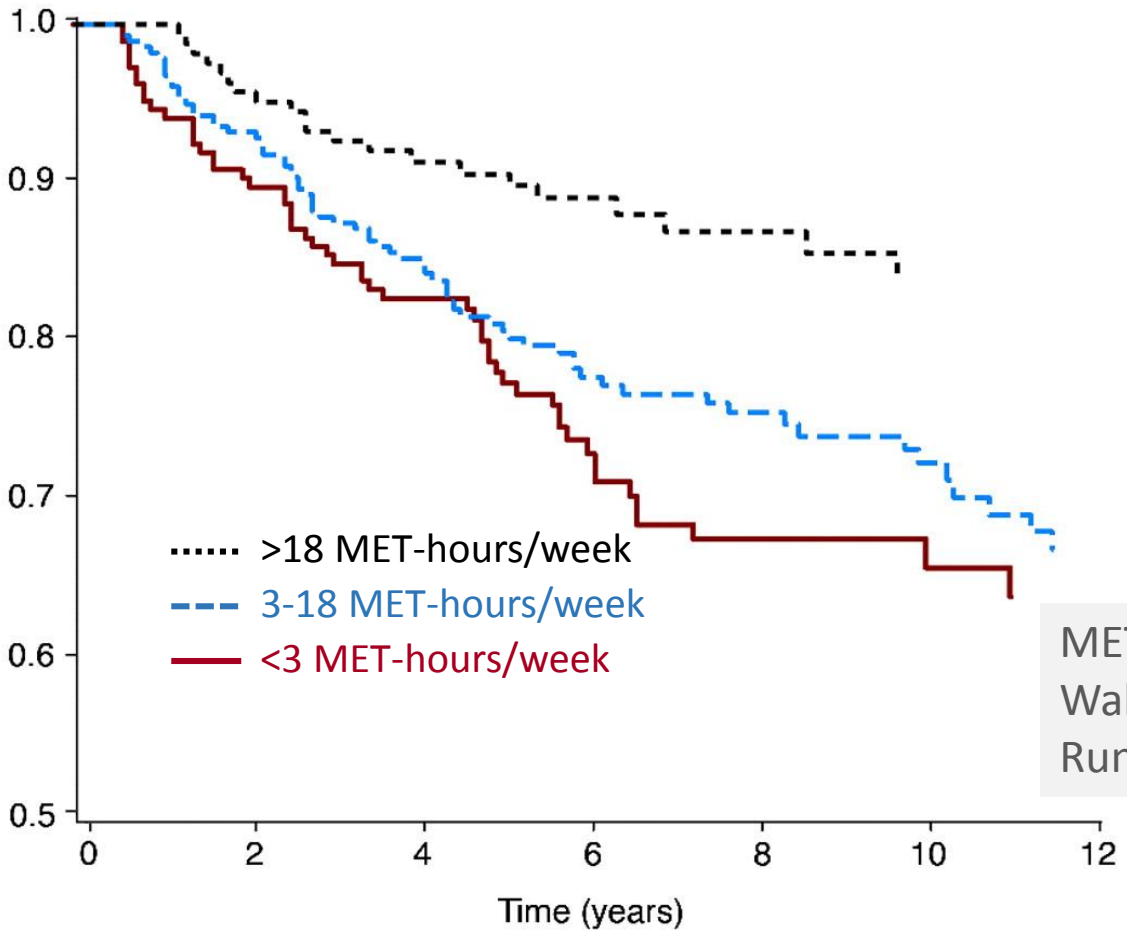


[1] Tucker et al., *Preventative Medicine*, 2017
[2] Robertson et al., *Cell Metabolism*, 2017
[3] Lee et al., *Progress in Cardiovascular Diseases*, 2017

Intense exercise significantly reduces cellular ageing and increases LE

Exercise also boosts cancer survival

Survival rates colorectal cancer (proportion alive)[1]



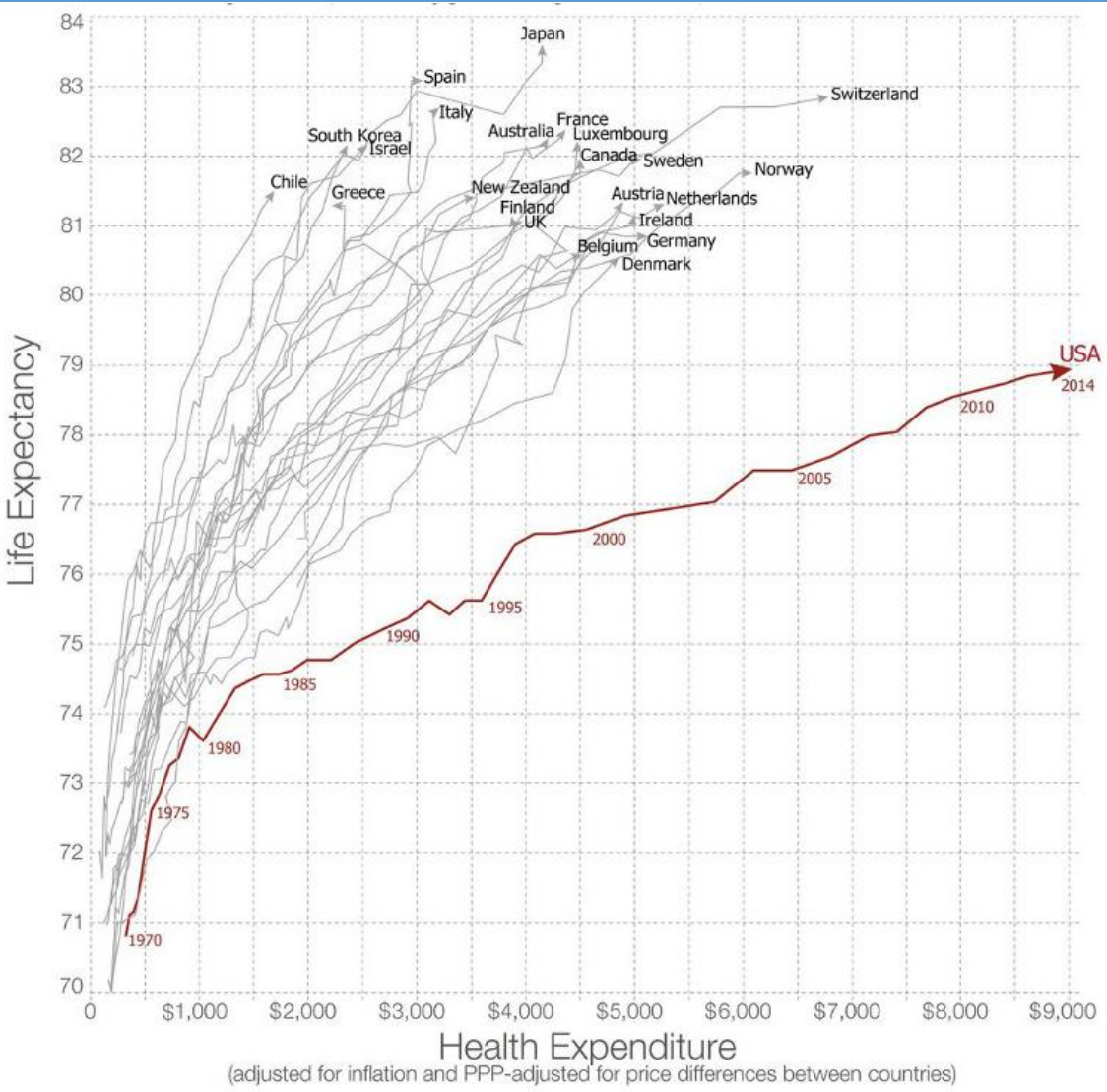
MET = Metabolic Equivalent
Walking = 3.3 METs
Running = 10 METs

[1] Meyerhardt et al J Clin Oncol 2006

Again, the more intense the exercise the better

Health environment: LE rises with health expenditure

Life expectancy vs. health expenditure 1970-2014



Health environment: Pollution impact

- There is a negative correlation between LE and concentration of PM2.5 (particles <2.5 micrometres diameter)

US study 2009[1]	• 217 counties, 51 cities • Reducing concentration of PM2.5 by 10 micrograms per cubic metre increased LE by 0.77 years
Similar Western studies	• Increase in concentration by this amount reduces LE: ○ Netherlands: 1.1 years ○ Finland: 1.37 years ○ Canada: 0.80 years
EPIC China study 2017[2]	• 154 cities over 2004-2012 • Difference in LE north vs south of Huai river: 3.1 years • Due to air pollution from coal burning

[1] Pope et al., NEJM 2009
[2] Ebenstein et al., PNAS 2017

There are significant LE benefits from clean air

Even regulators are predicting a step-change in the impact of medical science

"New technologies … hold out the potential to transform medicine and create an inflection point in our ability to treat and even cure many intractable illnesses."

FDA Commissioner Scott Gottlieb, M.D.
30 August 2017

Immunotherapy has been generating headlines

FDA U.S. FOOD & DRUG ADMINISTRATION

30 August 2017

FDA News Release

FDA approval brings first gene therapy to the United States

CAR T-cell therapy approved to treat certain children and young adults with B-cell acute lymphoblastic leukemia

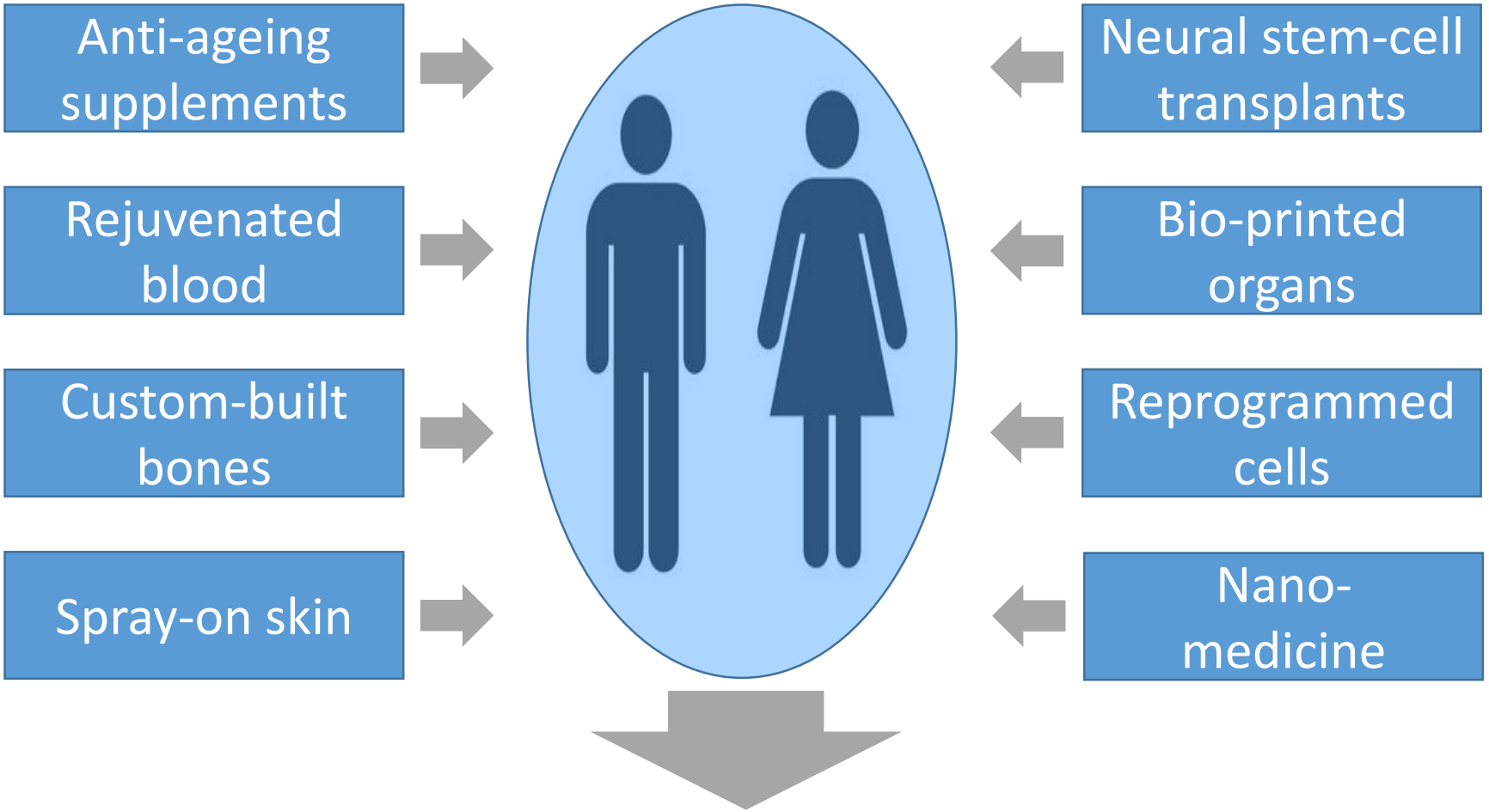
Cost: $475,000

Photo: Novartis

"We're entering a new frontier in medical innovation with the ability to reprogram a patient's own cells to attack a deadly cancer."

FDA Commissioner Scott Gottlieb, M.D.

New frontiers:
Regenerative medicine and anti-ageing research



Significantly increased life expectancy(?)

Regenerative medicine embraces many approaches

- A multi-disciplinary approach involving methods to regrow, repair or replace damaged/diseased cells, organs or tissues

Tissue engineering	Customised materials (cells and synthetics) to replace injured or diseased tissues
Cell therapy	Getting cells to grow into different kinds of tissue to heal an injury or cure a disease
Artificial organs	Keep patients alive while they await a donor organ, and sometimes eliminate the need for a transplant
Other therapies	Individualised gene therapy, nanomedicine

Tissue engineering has been making steady – but not black-swan-like – progress

Medical Xpress

Diabetics get blood vessels made from donor cells

June 27, 2011 By MARILYNN MARCHIONE , AP Medical Writer

2011

Medical Daily

Esophagus Grown And Transplanted With Tissue Engineering In Regenerative Medicine Breakthrough

Apr 15, 2014 04:22 PM By John Ericson

2014

European Commission

RESEARCH & INNOVATION

HORIZON
The EU Research & Innovation Magazine

Living heart valves grown in laboratories

12 November 2015

2015

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Cell therapy is making significant progress

- Induced Pluripotent Stem cells (iPS cells) are 10 years old
  - Stem cells from other cells e.g., ordinary skin cells

Retinal cells	• Treatment for blindness, macular degeneration • Clinical trials are underway
Blood platelets	• Mass production now possible • Treatments for cancer, trauma, transplants, surgery • Clinical trials Japan, US 2018, Europe 2019
Neurons	• Treatment for Parkinson's disease • Successful animal trials completed with monkeys

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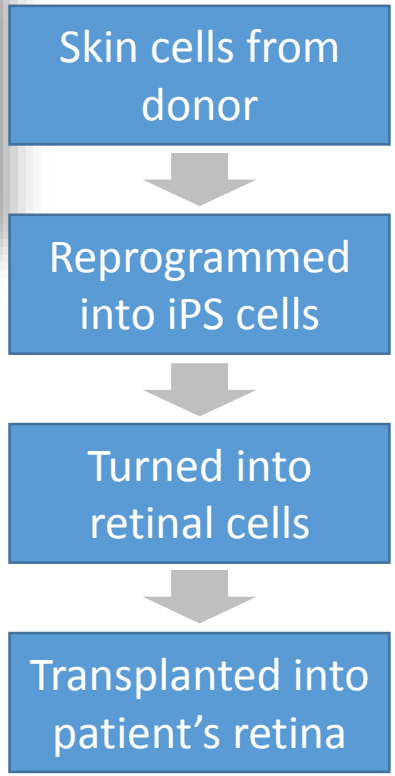
Recent breakthrough:
Reprogrammed retinal cells transplanted from donor

nature International weekly journal of science

28 March 2017

Japanese man is first to receive 'reprogrammed' stem cells from another person

World-first transplant, used to treat macular degeneration, represents a major step forward in movement to create banks of ready-made stem cells.



➔Treatment to arrest age-related macular degeneration

- In 2014 a Japanese woman underwent similar procedure, but using her own skin cells
- A year later, her vision had not deteriorated further

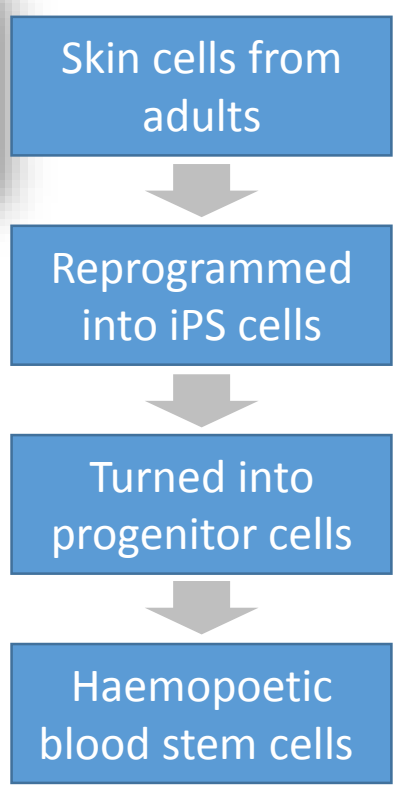
Recent breakthrough: Production of blood stem cells

nature International weekly journal of science

17 May 2017

Lab-grown blood stem cells produced at last

Two research teams cook up recipe to make long-sought cells in mice and people.



➔Treatment leukaemia and other blood disorders

- Mature cells transformed into primordial blood cells that regenerate themselves and the components of blood.

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Recent breakthrough:
Therapies to reverse age-related cognitive decline

PNAS

8 August 2017

Proceedings of the National Academy of Sciences of the United States of America

Arc restores juvenile plasticity in adult mouse visual cortex

A single gene "Arc" can rejuvenate the plasticity of the mouse brain.

nature International weekly journal of science

30 Aug 2017

Reprogrammed cells relieve Parkinson's symptoms in trials

Monkeys implanted with neurons derived from stem cells showed sustained improvement after two years.

Anti-ageing: Many interventions have been highly successful in extending lifespans of lab animals

- Caloric restriction
- “Fasting mimicking diet” (FMD)
- Dietary supplements (drugs)
- Tweaking genes
- Repressing inflammation genes in the brain
- Transfusing blood of the young into the old
- Extension of telomeres
- Senescent cell removal

Recent breakthroughs: Advances in anti-ageing treatments

nature International weekly journal of science

3 Feb 2016

Destroying worn-out cells makes mice live longer

Elegant experiment confirms that targeting senescent cells could treat age-related diseases.

- 25% increase in median life span
- Heathier

TIME | Health

23 Mar 2017

Scientists Can Reverse DNA Aging in Mice

- Repair DNA damage due to age or radiation
- NASA is interested

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Can success with animals be translated into humans?

For round worms *(C. elegens)* scientists have achieved a 10-fold increase in lifespan!

- The round worm has only 959 cells
  - Yet over 550 genes have been found to modulate lifespan
- Humans are much, much more complicated

Despite the hype, our best estimate is we still have a long way to go

Very smart, very successful people with huge resources are turning to the challenge of extending life

Exclusive: TIME Talks to Google CEO Larry Page About Its New Venture to Extend Human Life

Bold project, to be led by biotech pioneer Arthur Levinson, will tackle's some of health care's biggest problems

By TIME Staff | Sept. 18, 2013

TIME

The Obsession With 'Curing' Aging Is Now Big Business

by Laura Lorenzetti @lauralorenzetti MARCH 7, 2016, 6:00 AM EST

Tech titans bankrolling it.

FORTUNE

1. Peter Thiel – Founder of PayPal
2. Bill Maris – President "Google Ventures"
3. Arthur Levinson – ex-CEO & Chief Scientist Genentech; CEO Google's "Calico"
4. Dave Gobel – co-founder of the Methuselah Foundation
5. Craig Venter – Key contributor to first human genome decoding
6. Martine Rothblatt – Founder Sirius Satellite Radio; CEO United Therapeutics

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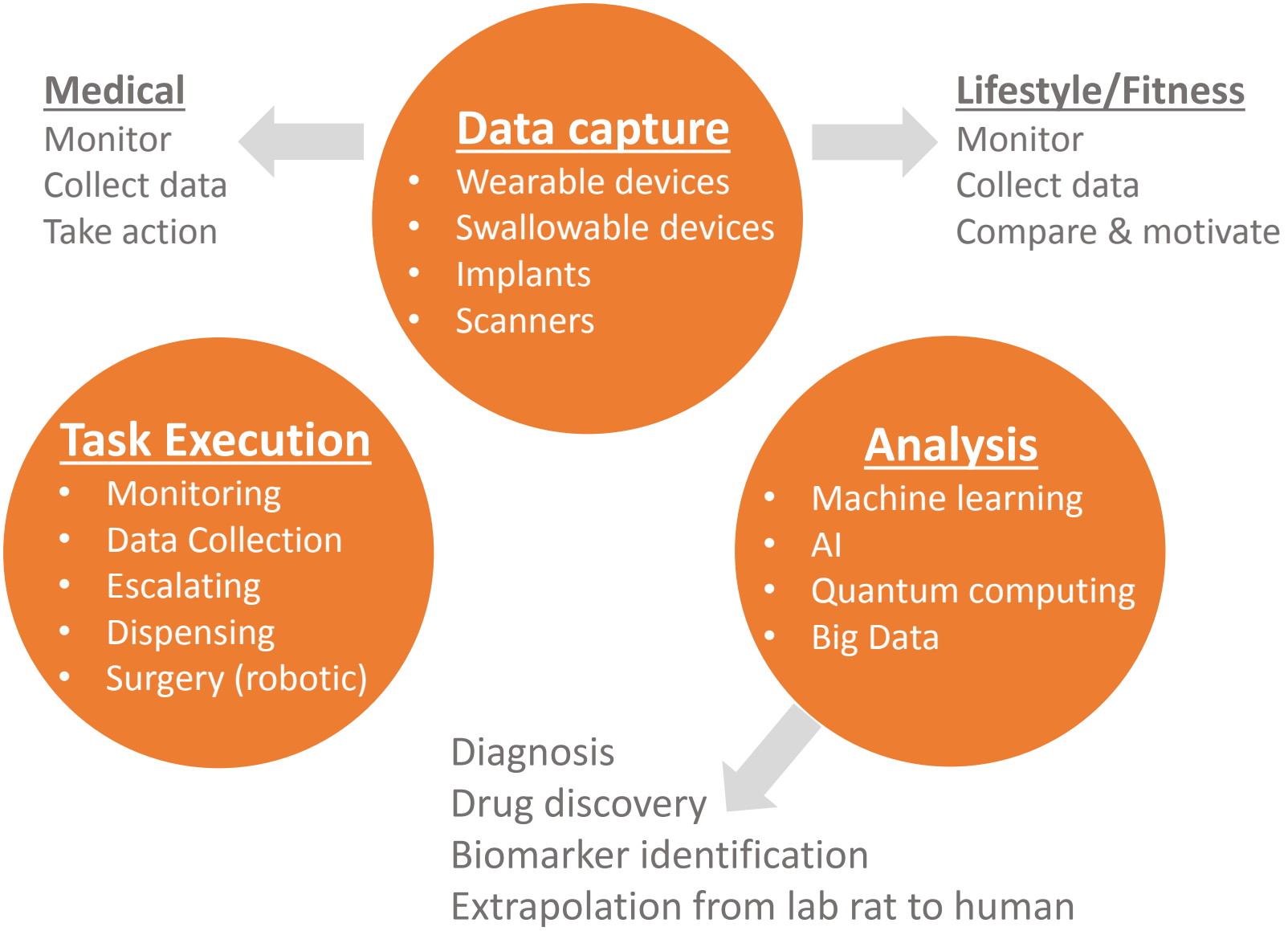
The role of technology in increasing life expectancy is multifaceted



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Longevity predictions offer divergent future scenarios

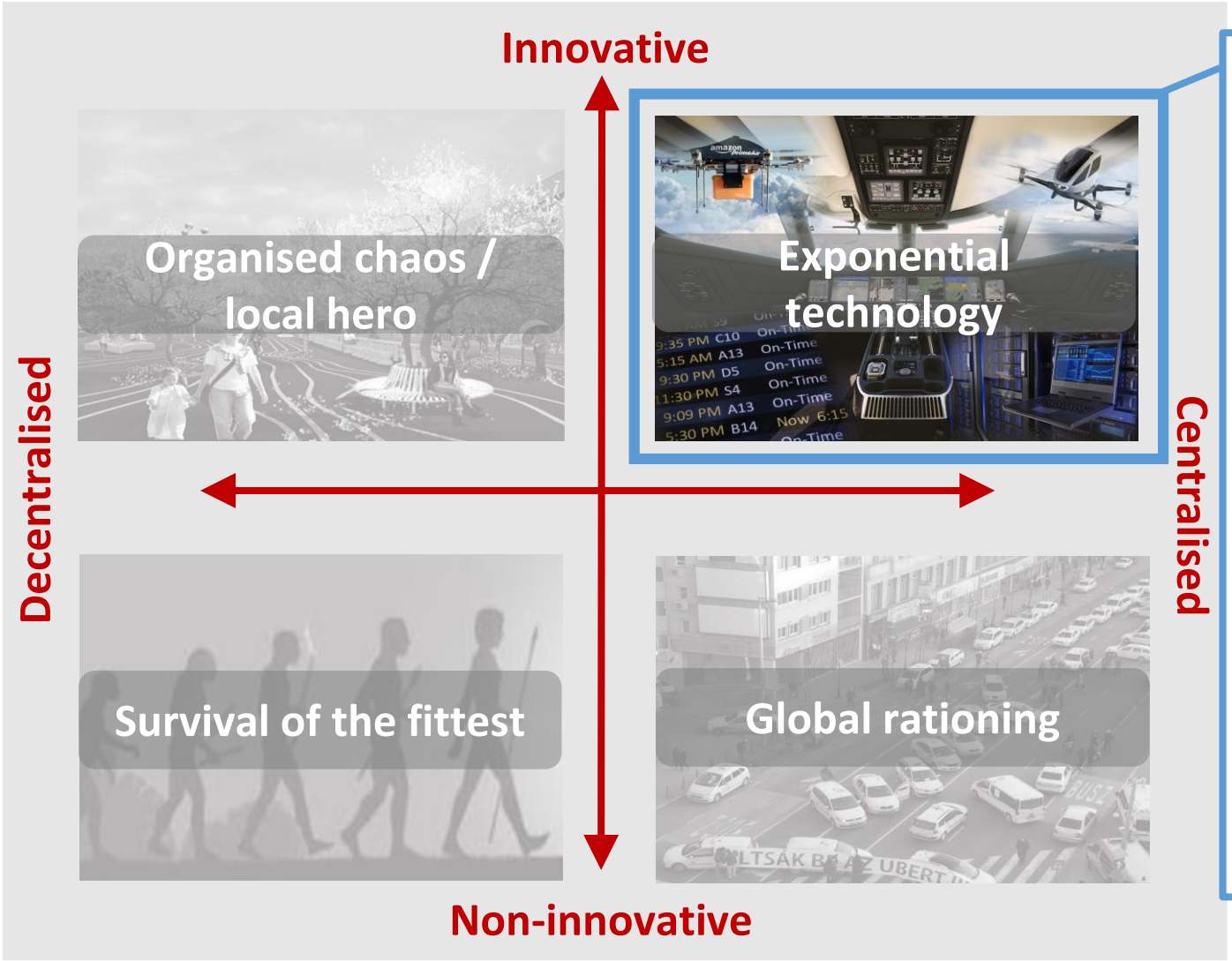
Exponential Growth?

"What I'm after is not living to 1,000. I'm after letting people avoid death for as long as they want to."
Aubrey De Grey

Stagnation?

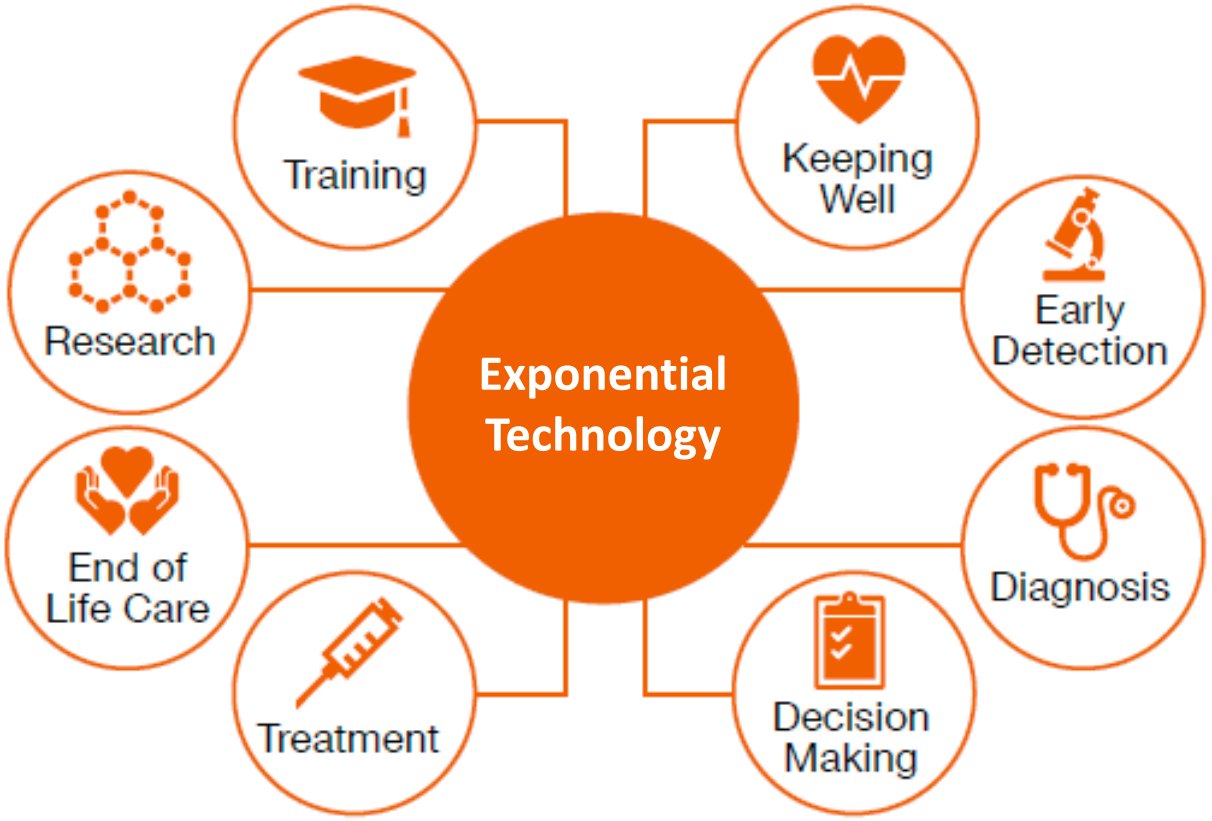
"While eliminating smallpox and curtailing cholera added decades of life to vast populations, cures for the chronic diseases of old age cannot have the same effect on life expectancy. A cure for cancer would be miraculous and welcome, but it would lead to only a three-year increase in life expectancy at birth."
S. Jay Olshansky

A scenario: “Exponential technology”

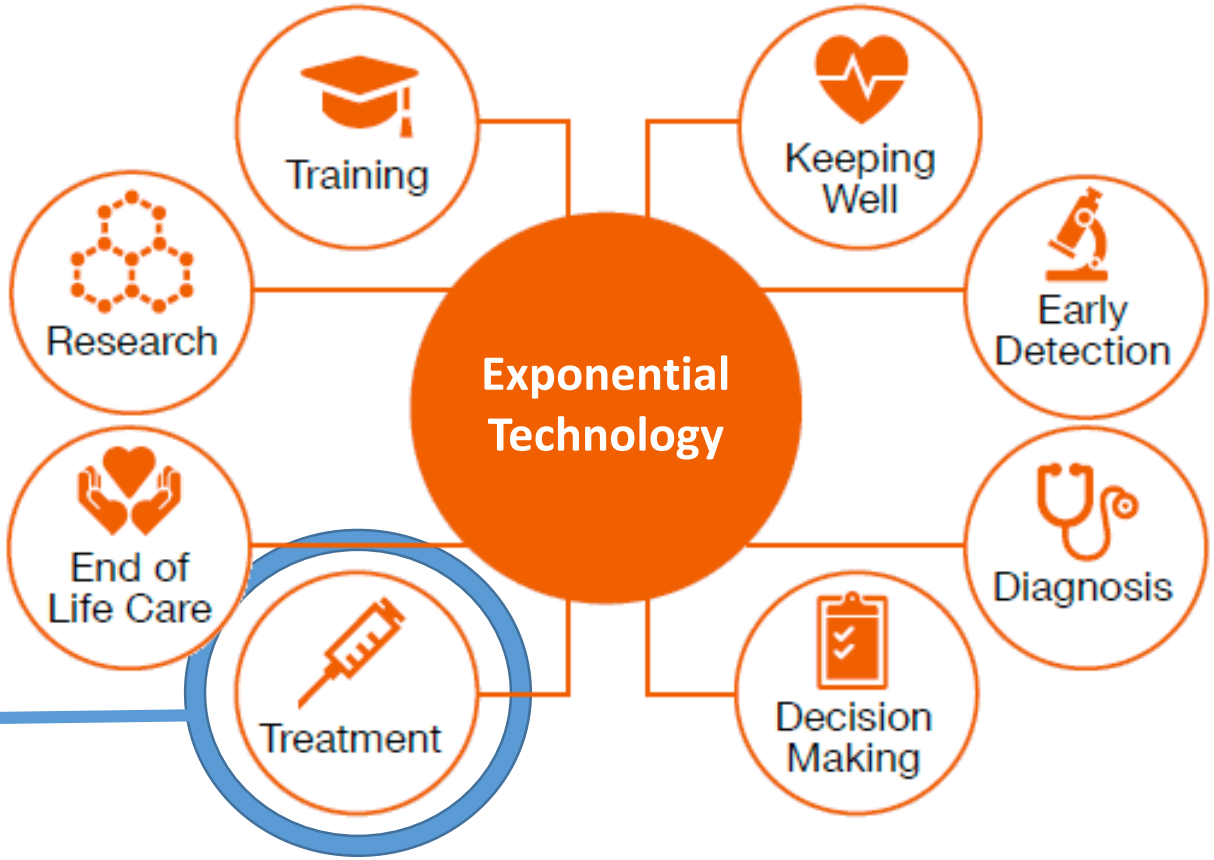


- **Economic** – machines and automation replace traditional roles to make work more productive and efficient.
- **Technological** – science-led sectors such as AI, 3D printing and autonomous vehicles experience exponential growth.
- **Social** – increased inequality, new tools being required to maintain harmony.
- **Political** – governance takes new forms with control through the state and data.

Drivers of longevity growth

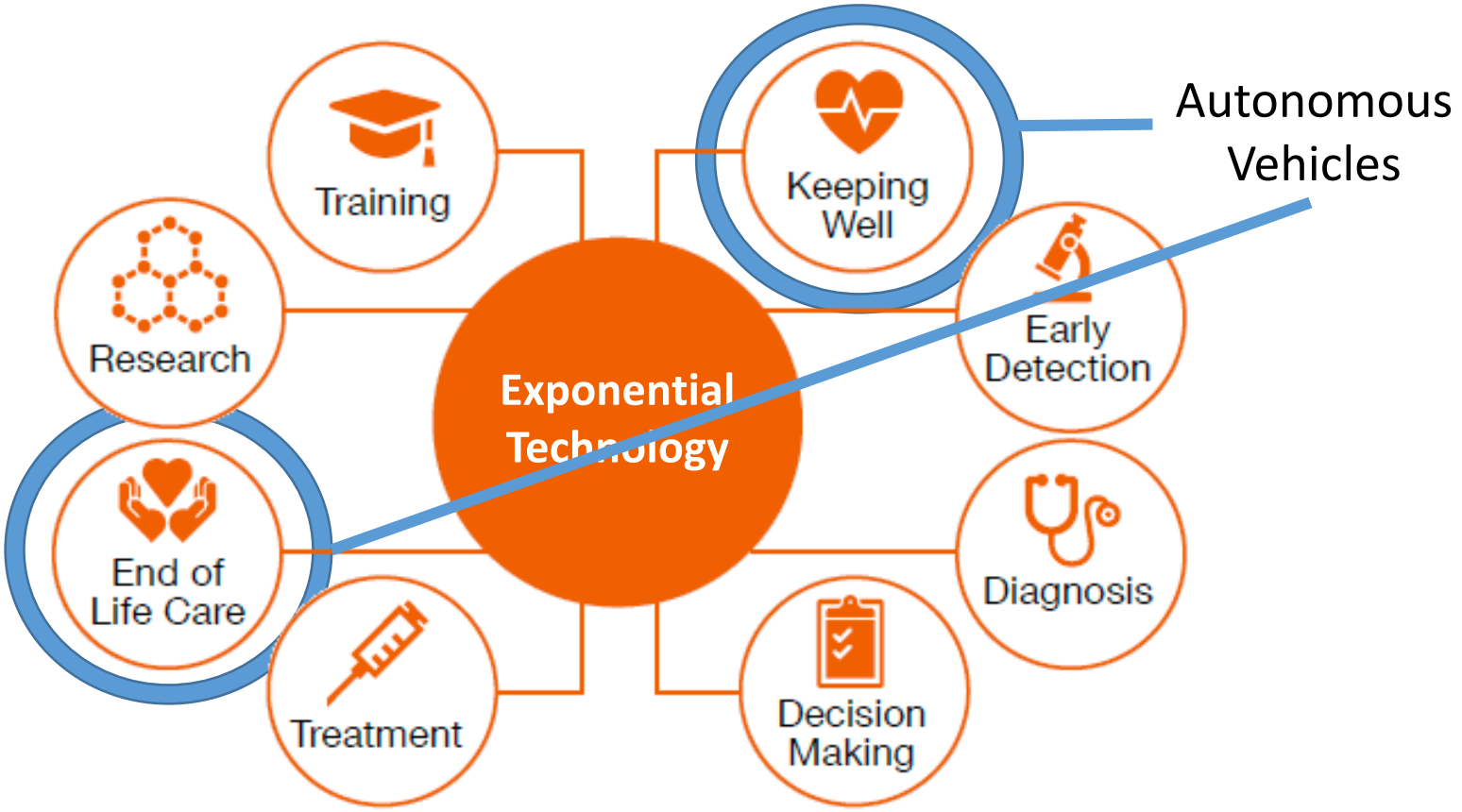


Drivers of longevity growth

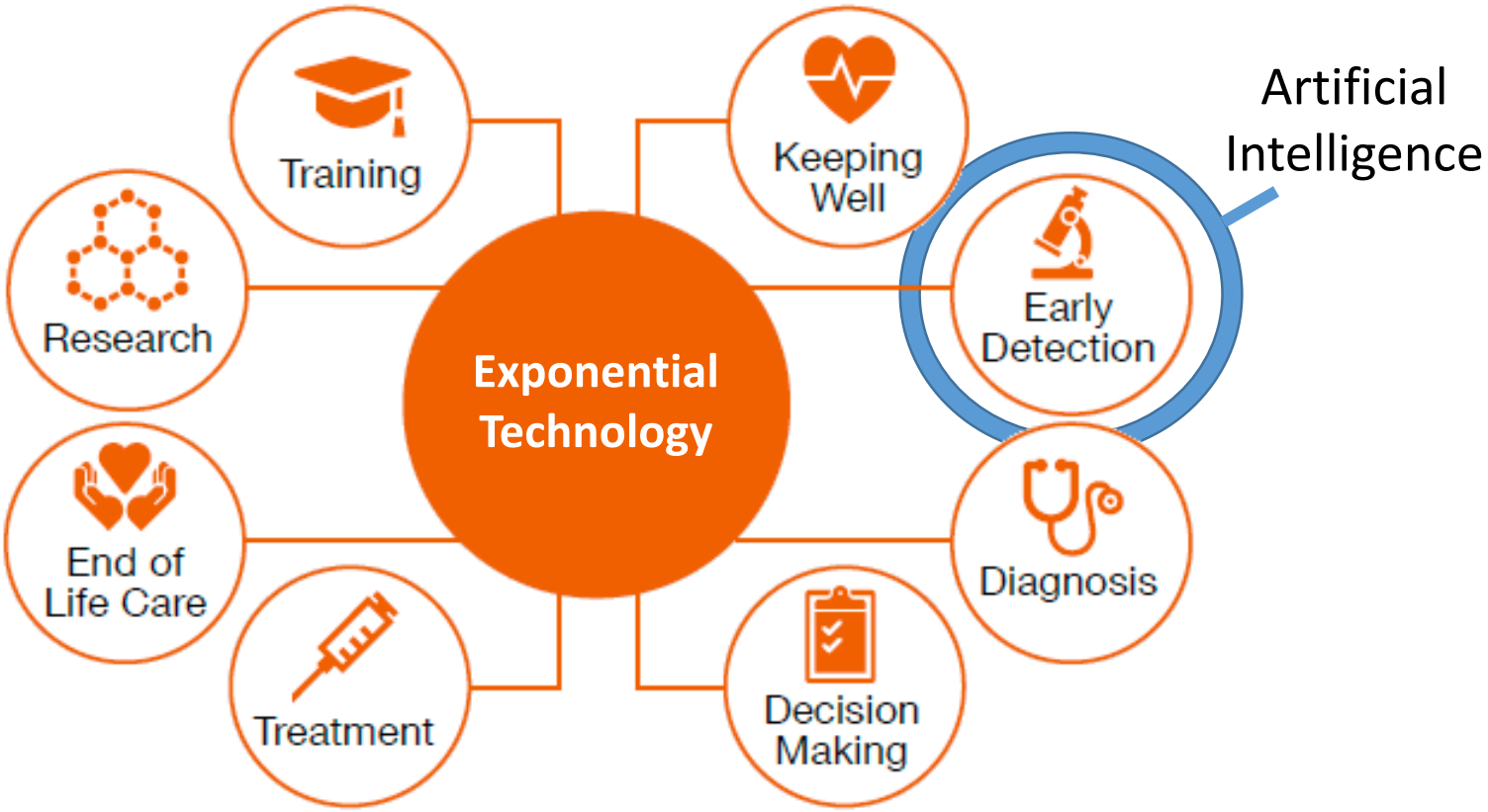


3D Printing of organs

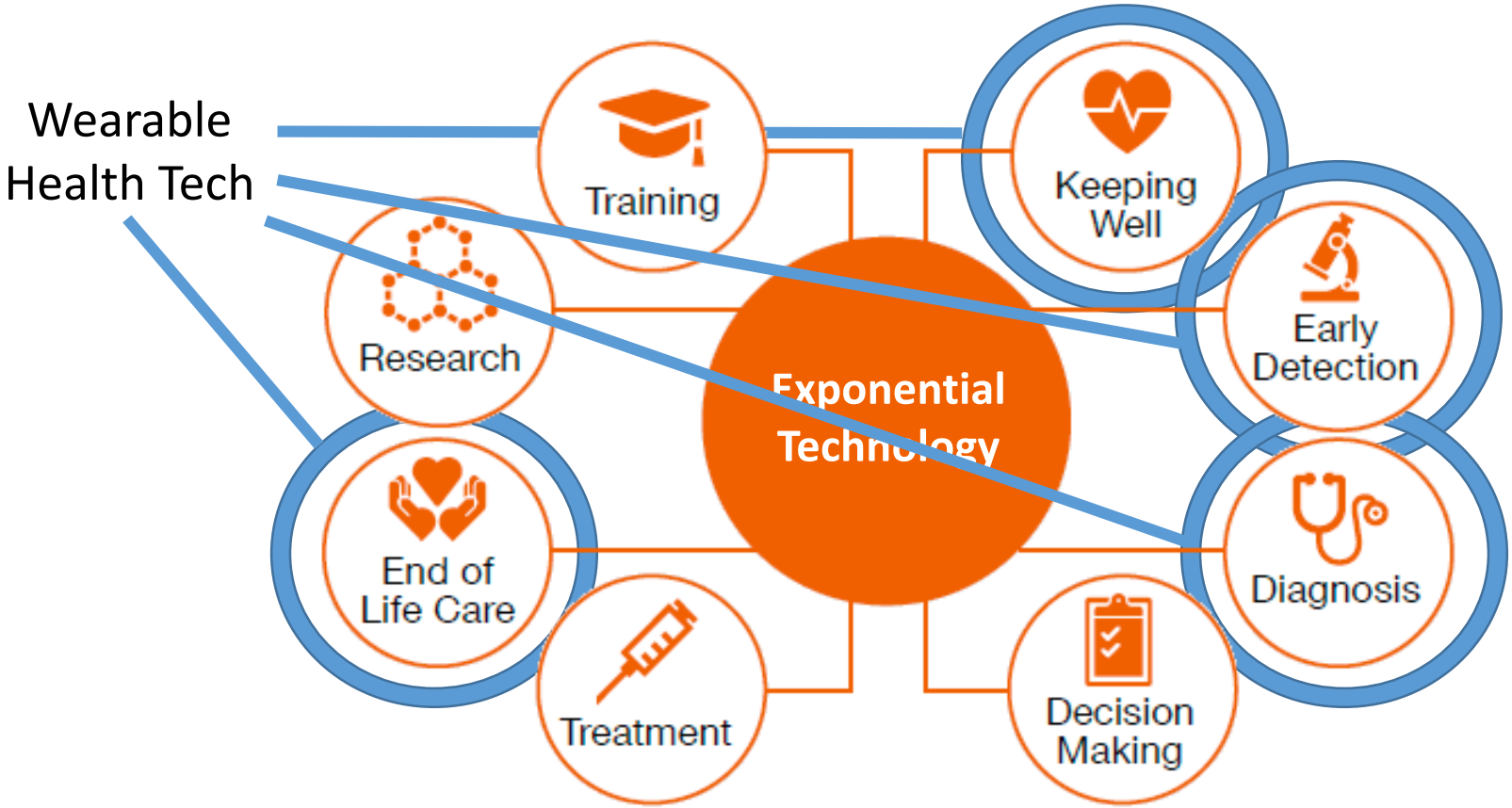
Drivers of longevity growth



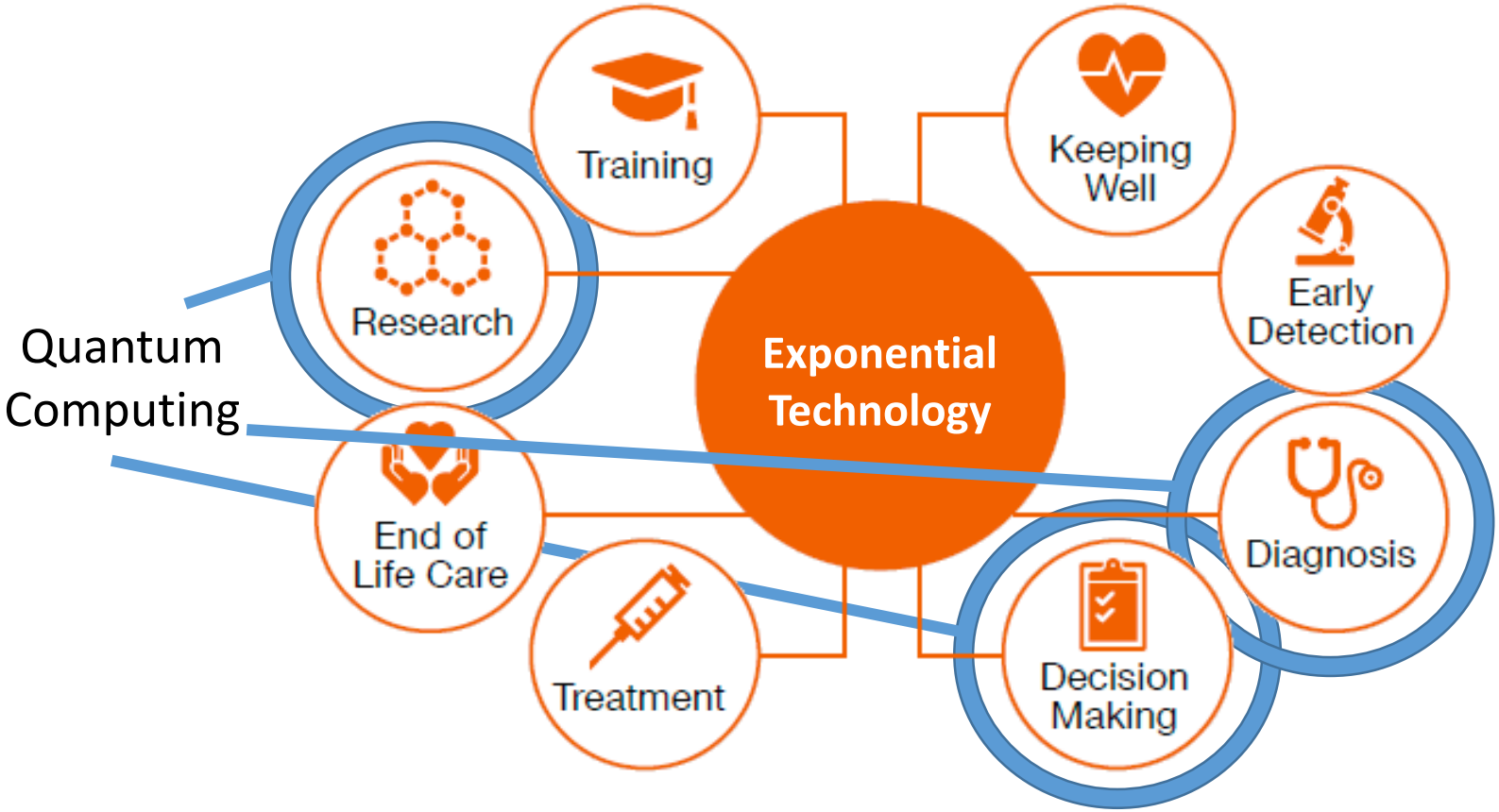
Drivers of longevity growth



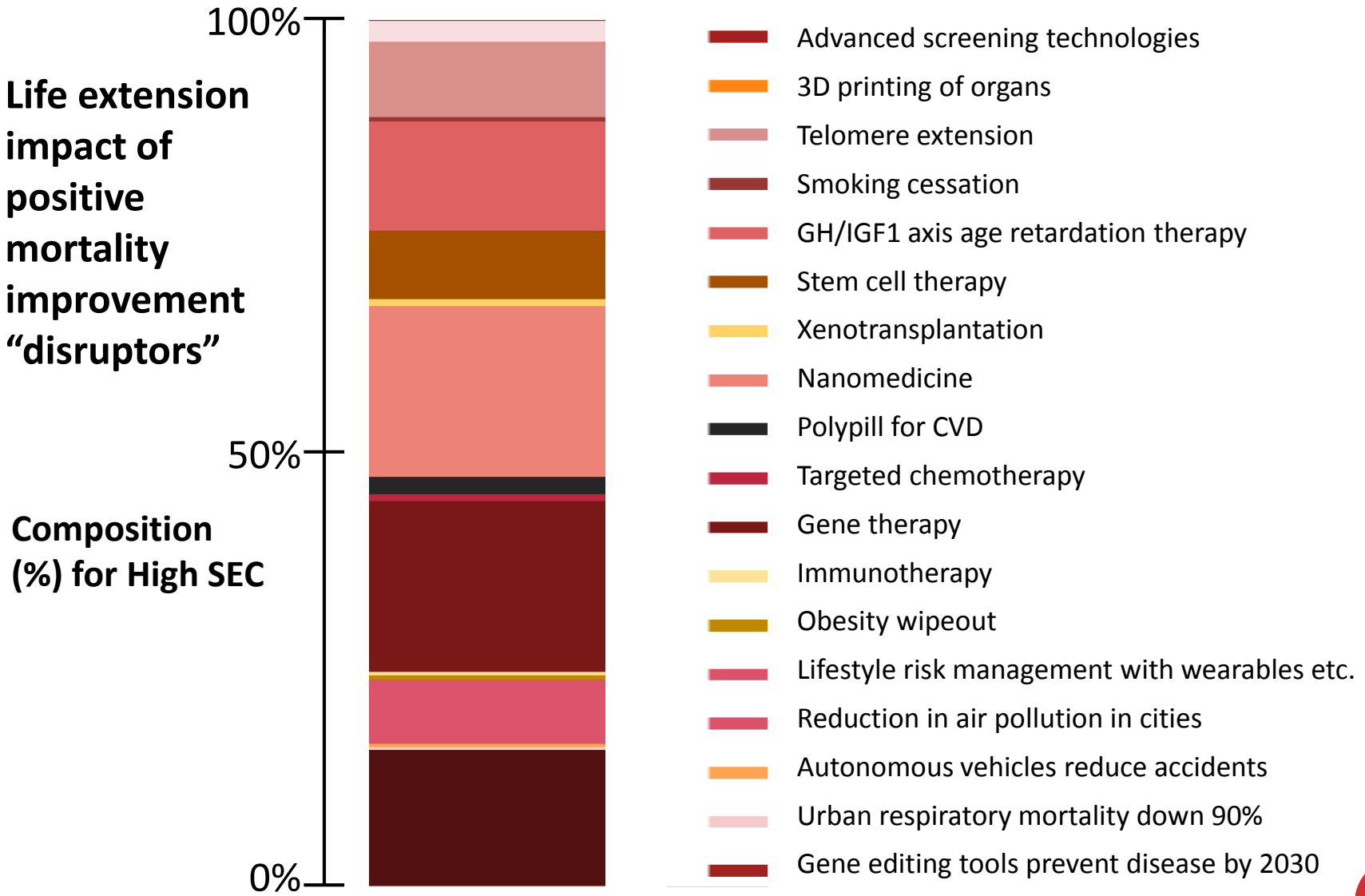
Drivers of longevity growth



Drivers of longevity growth



What is the potential impact on life extension of positive "disruptors" for mortality improvements



Mapping positive and negative mortality "disruptors"

Environment

Electric/Autonomous Vehicles & Air Quality Improvements

Isolation & Depression

Public Healthcare Investment Crisis

Health Intervention

Gene editing/manipulation

3D Organ Printing

Xenotransplantation

Regenerative Medicine

Stem Cell Therapy

Nanomedicine

Personalised Medicine

Gene Therapy

Immunotherapy

Polypill

GH/IGF1 axis age retardation therapy

Genetic Screening

AI & Medical Advancement

Telemedicine & Accessibility to medical technologies

Nanomedicine risks

Increased costs of preventative care

Antibiotic Resistance

Lifestyle

Obesity Reduction

Telomere Extension

Lifestyle Risk Management: Wearables

Automation driven obesity

Vaping / smoking decrease

Disruptors will impact different Socio-Economic Classes (SECs) differently increasing inequality

	Environment	*Health Intervention*	*Lifestyle*
Highest Income Decile	Electric/Autonomous Vehicles & Air Quality Improvements	Gene editing/manipulation 3D Organ Printing Xenotransplantation Regenerative Medicine Stem Cell Therapy Nanomedicine Personalised Medicine Gene Therapy Immunotherapy GH/IGF1 axis age retardation therapy Polypill Genetic Screening	Obesity Reduction Telomere Extension Lifestyle Risk Management: Wearables
Lowest Income Decile	Isolation & Depression Public Healthcare Investment Crisis	AI & Medical Advancement Telemedicine & Accessibility to medical technologies Nanomedicine risks Increased costs of preventative care Antibiotic Resistance	Automation driven obesity Vaping / smoking decrease

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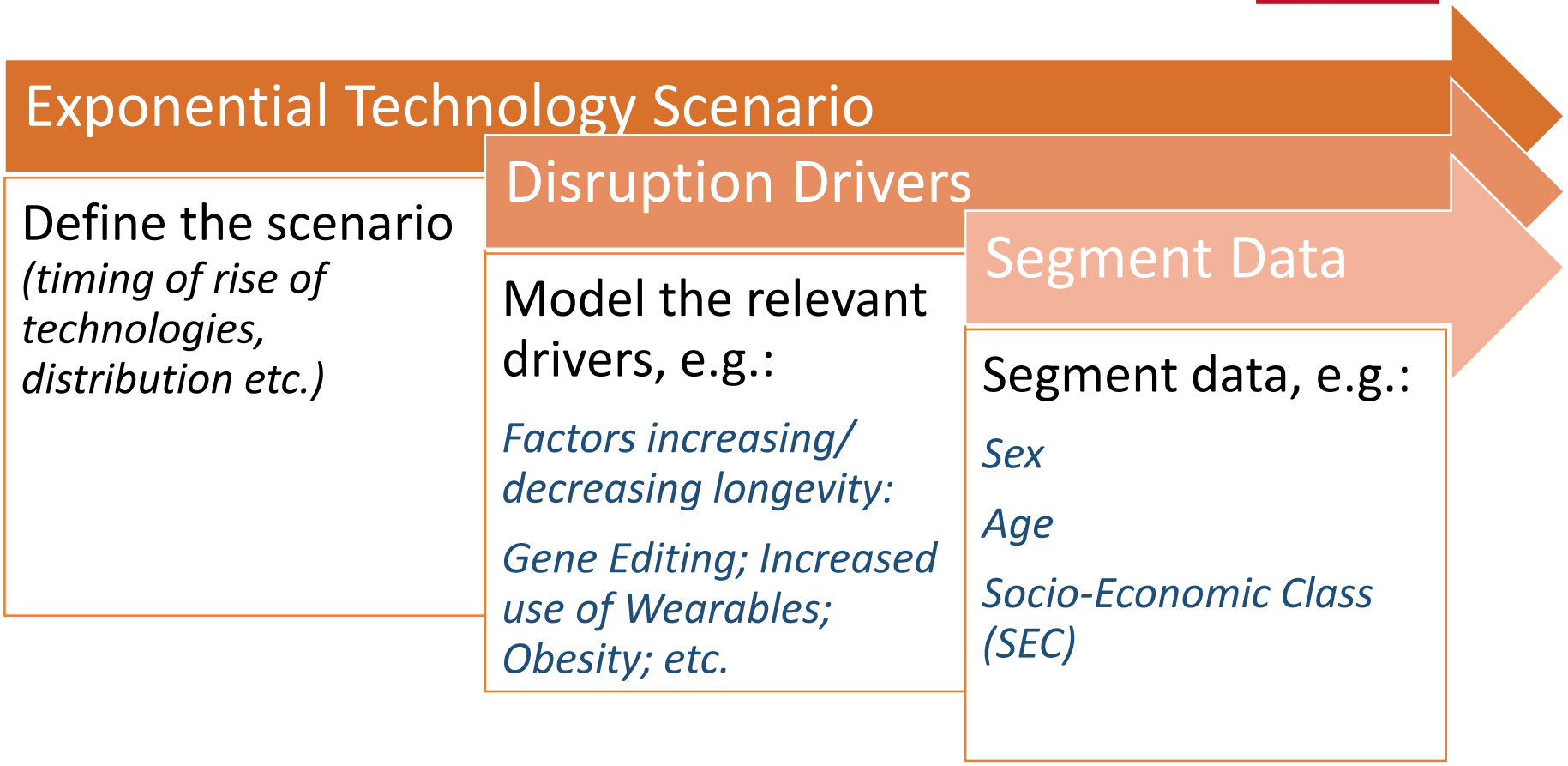
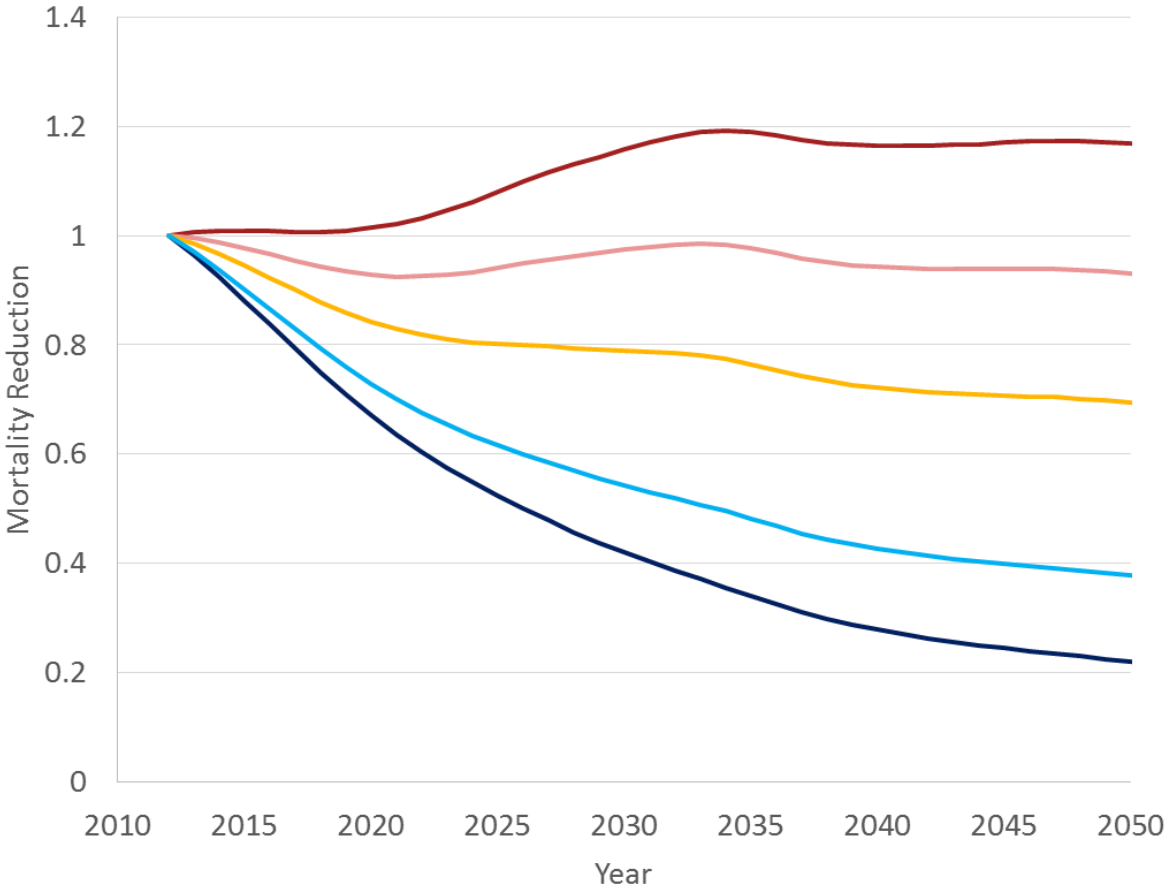
Modelling disruptive states for a population



Divergent mortality reductions experienced by different socio-economic classes (SECs)

Mortality reduction for a male aged 60 in 2017



Full stagnation

Low SEC **+28 years**

Medium SEC **+32 years**

High SEC **+39 years**

Full effect of exponential technology

Applied this model to measure the impact of the scenario on the liabilities of pension funds

Case study 1

	Low SEC	Medium SEC	High SEC	All
% liabilities	6%	28%	65%	-
Impact (%)	-11%	-3%	+10%	**+4%**

Case study 2

	Low SEC	Medium SEC	High SEC	All
% liabilities	0%	6%	94%	-
Impact (%)	-	-3%	+10%	**+9%**

Let us return to the original question:

Is there potential for significant extension of human lifespans?

- There are many scenarios that could potentially lead to a large extension to human life spans
- Technology is likely to play a central role in all of them
- The scenario we have explored is one possibility, but not the most extreme by a long way