Advances in Biogerontology: Clinical Promise and Ethical Pitfalls

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Department of Medicine

Live better longer

Who Am I?

Geroscientist at Buck Institute:

Metabolic signals that regulate aging

Geriatrician at UCSF:

Inpatient Medicine and Geriatrics

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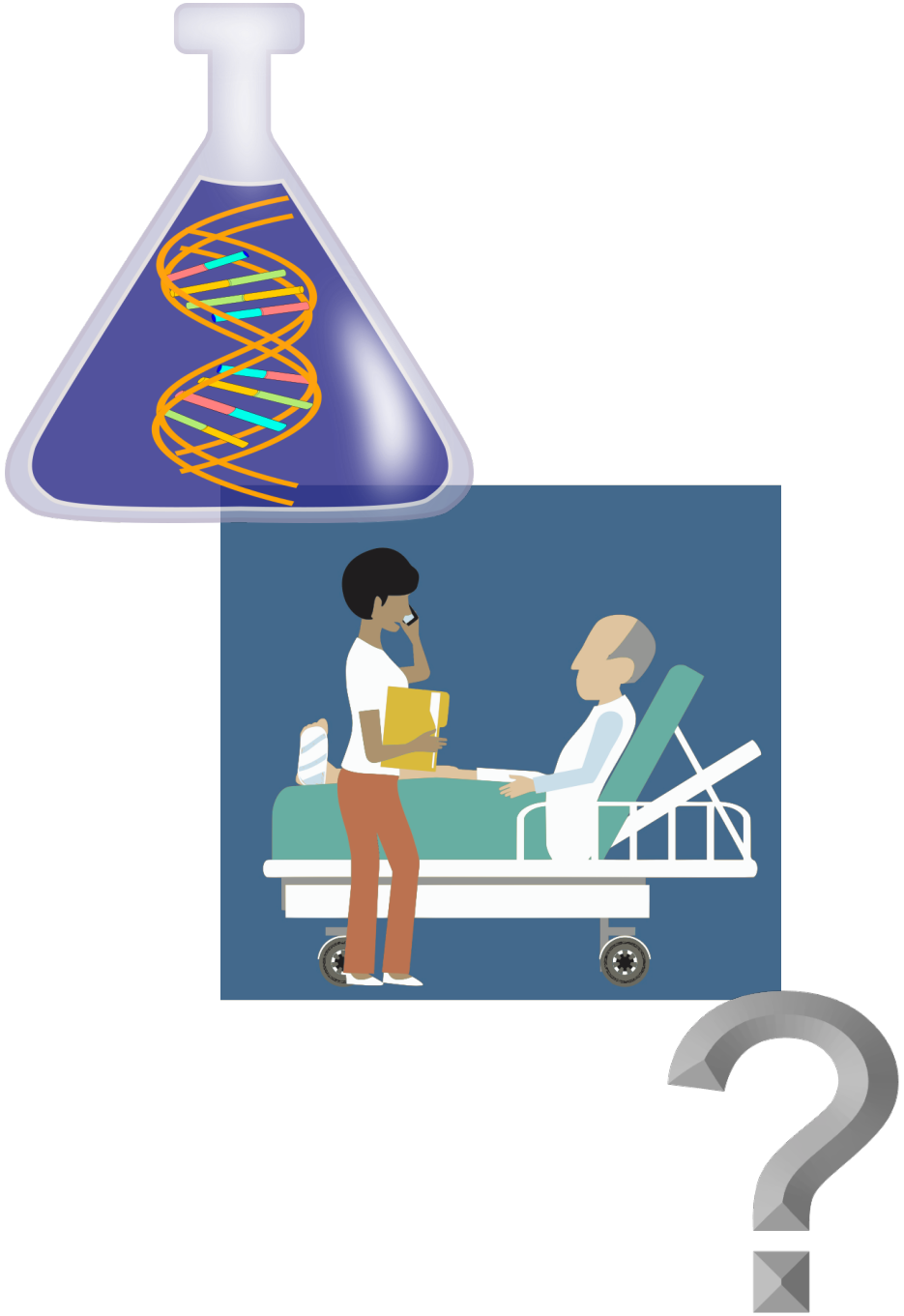
@GeriSciDoc

Part 1: Aging Biology

Part 2: Clinical Trials

Part 3: Questions



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Part 2: Clinical Trials

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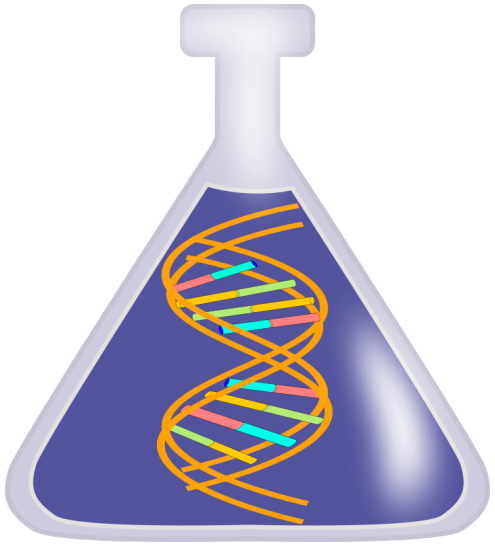

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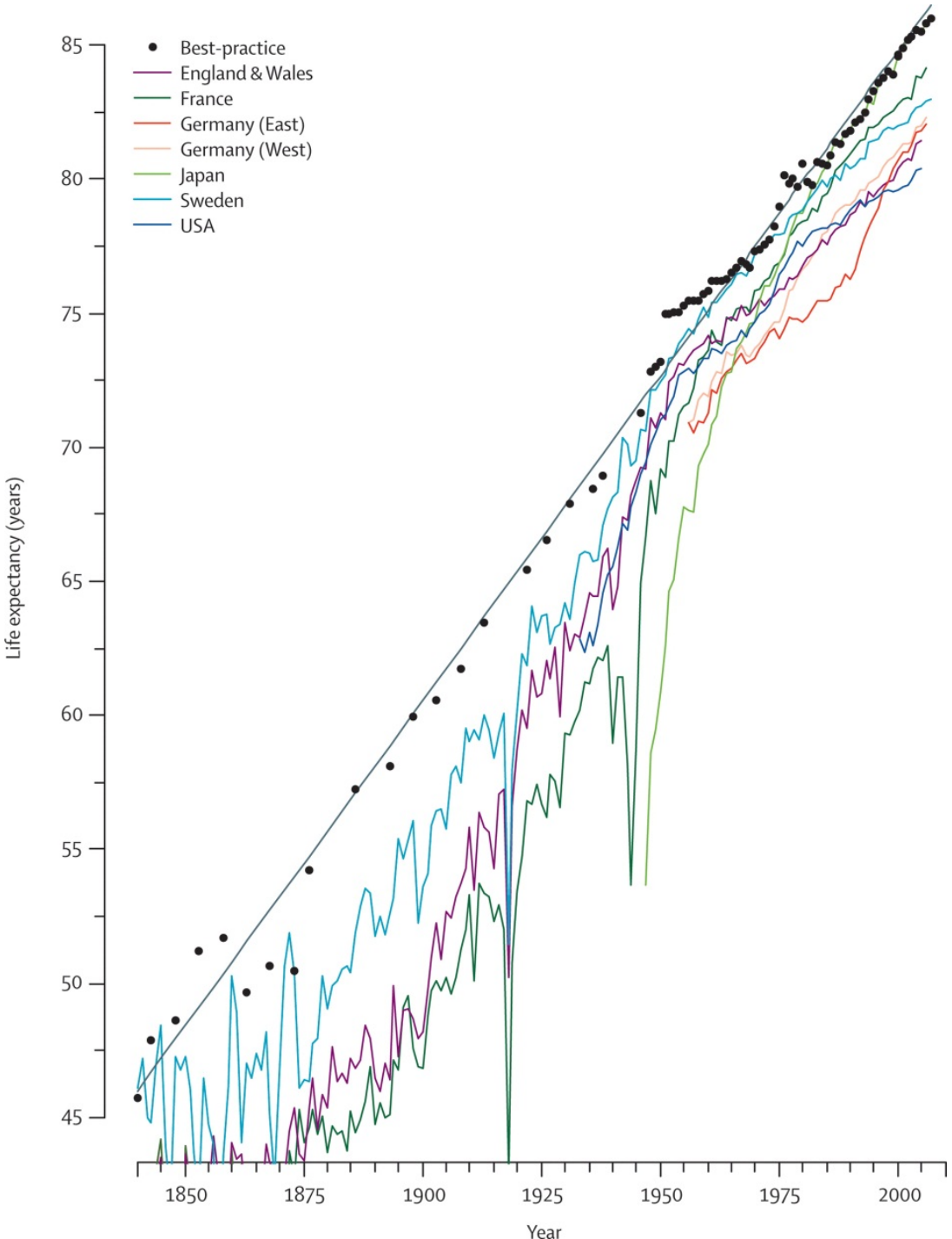
The Longevity Revolution: An old story!



Since 1850,
life expectancy has advanced by one year for every four
(“Christensen’s Law”?)

Christensen et al.,
Lancet 2009

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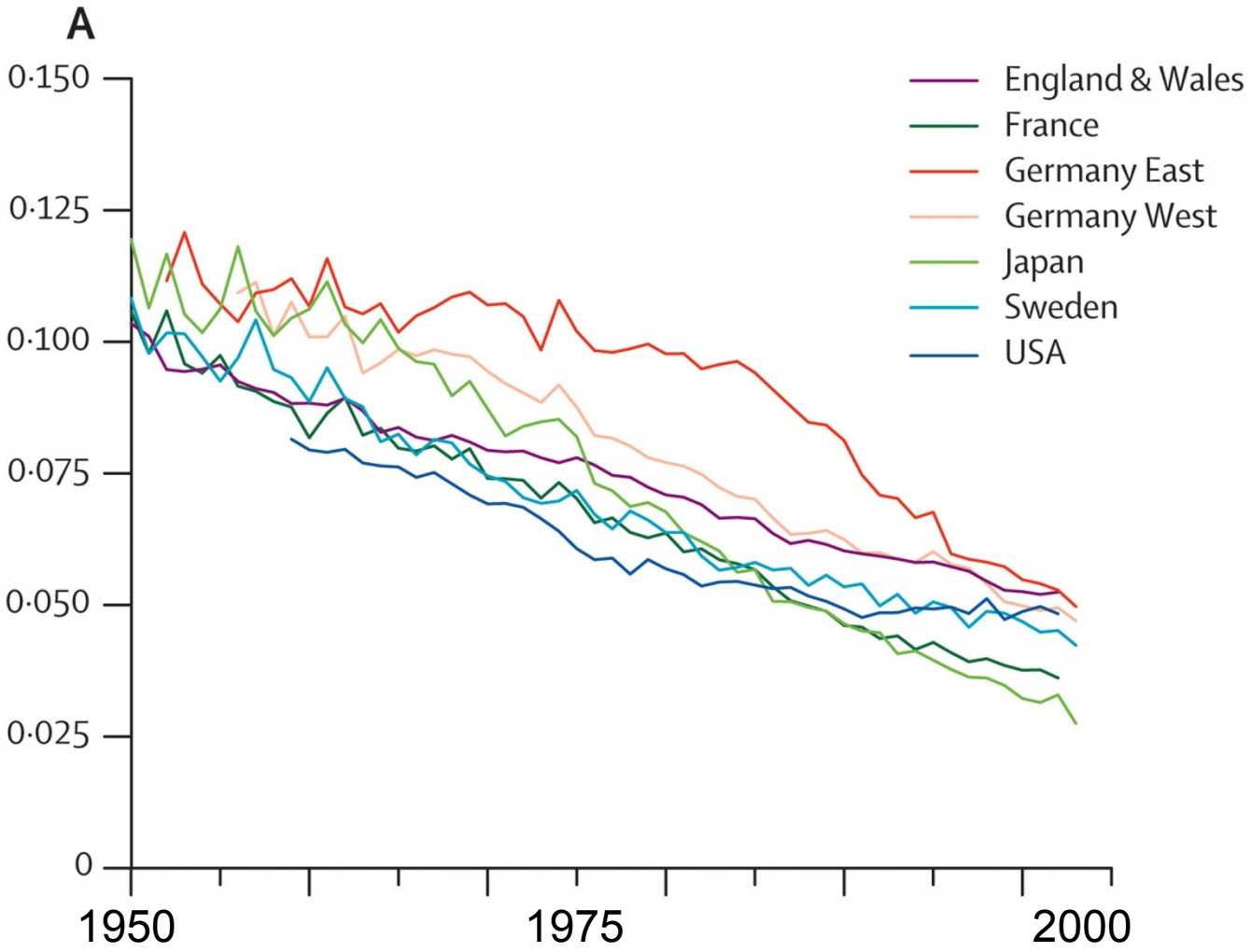
The Longevity Revolution: An old story!



Chance of dying while age 80

Mortality is falling throughout life, even among the very oldest

Christensen et al., Lancet 2009

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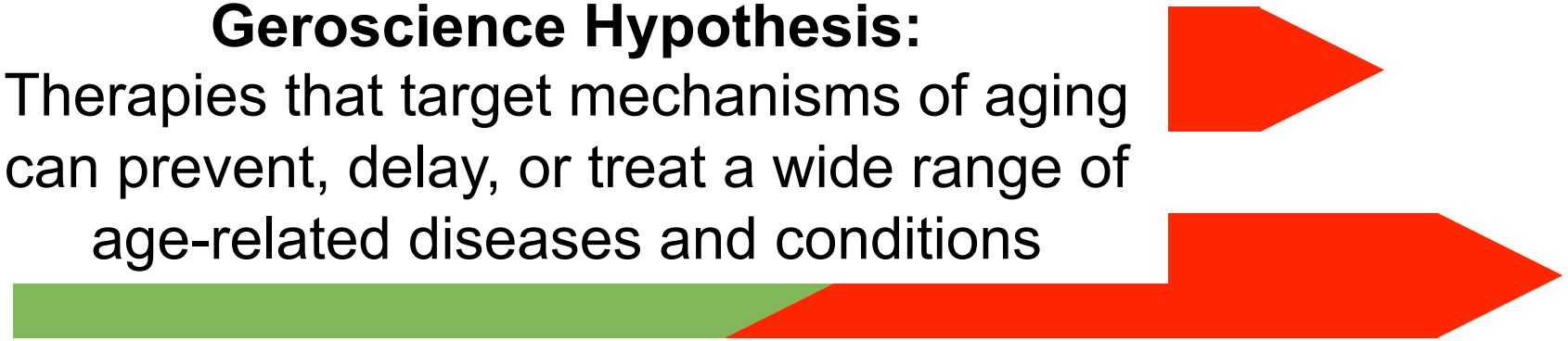
Healthspan

Healthy life Illness and disability

Geroscience Hypothesis:
Therapies that target mechanisms of aging can prevent, delay, or treat a wide range of age-related diseases and conditions

Extend lifespan



Extend healthspan

Extend both

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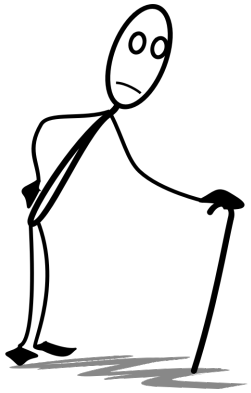
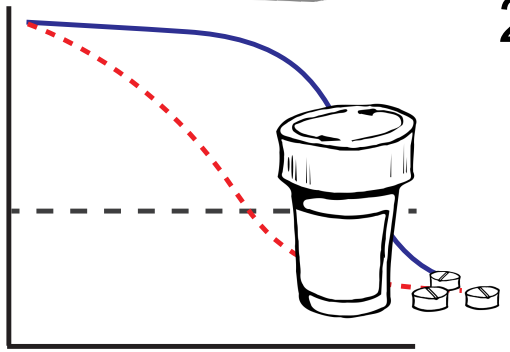
How to study “Aging”



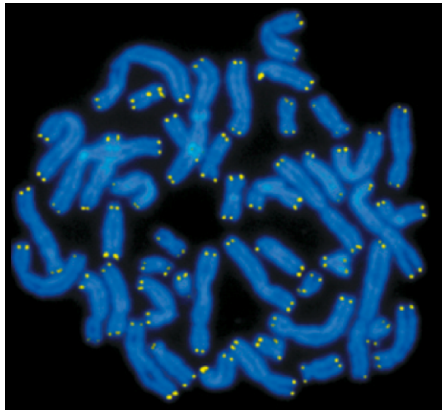


1. Describe it

   Gradual, progressive, universal loss of function beginning after maturation

2. Define it

   Susceptibility to disease
   Increasing probability of death
   Loss of resilience to stressors
   Loss of reproduction capacity



3. Operationalize it for studies

   Cell divisions
   Lifespan
   Multimorbidity

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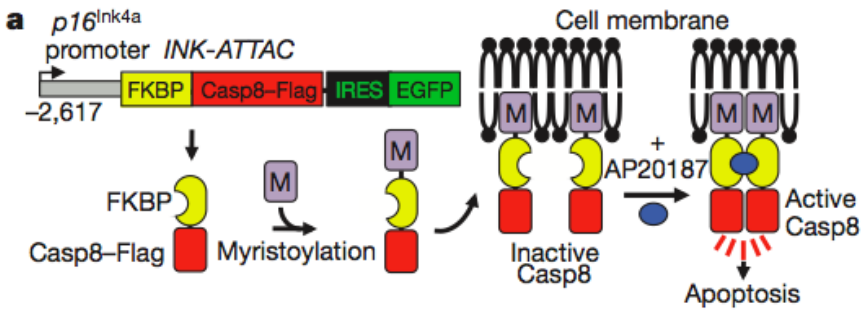
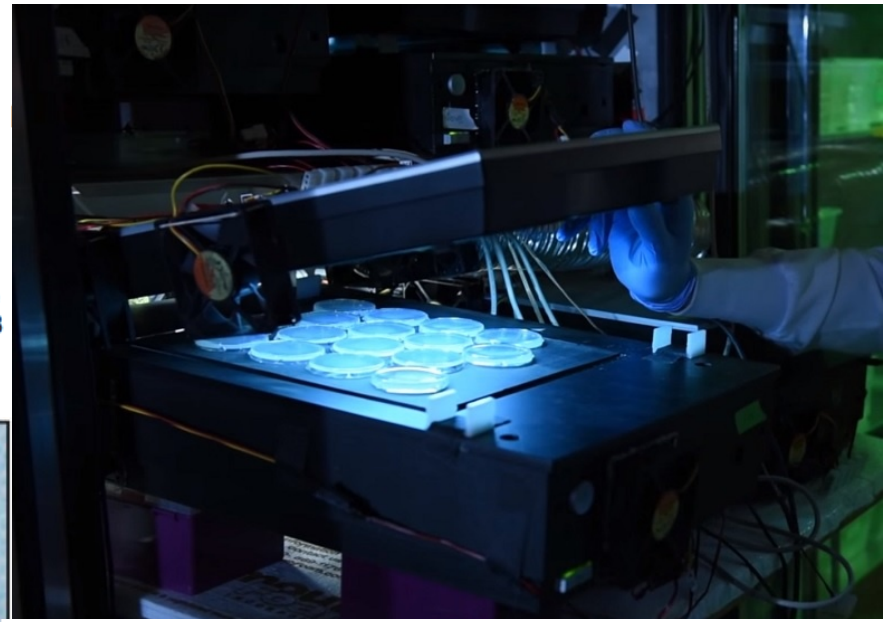
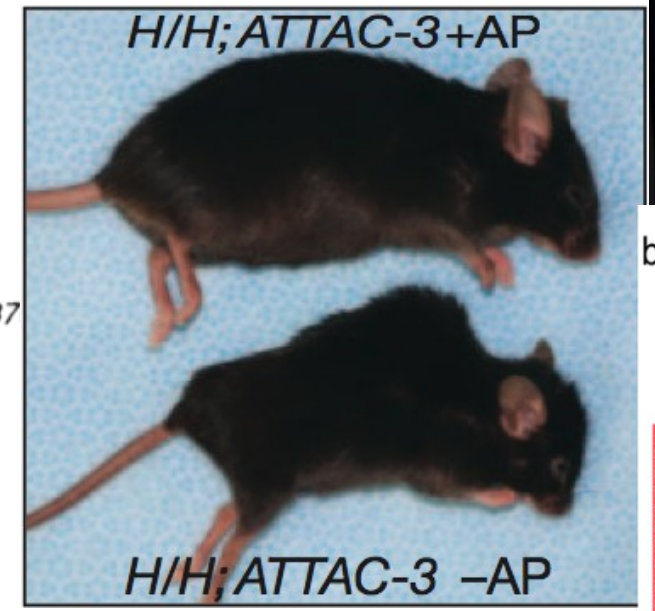
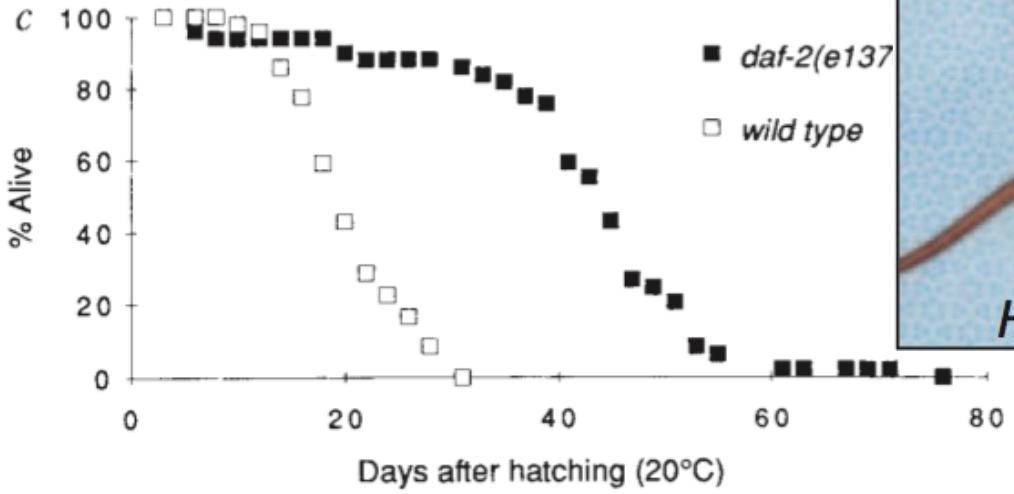
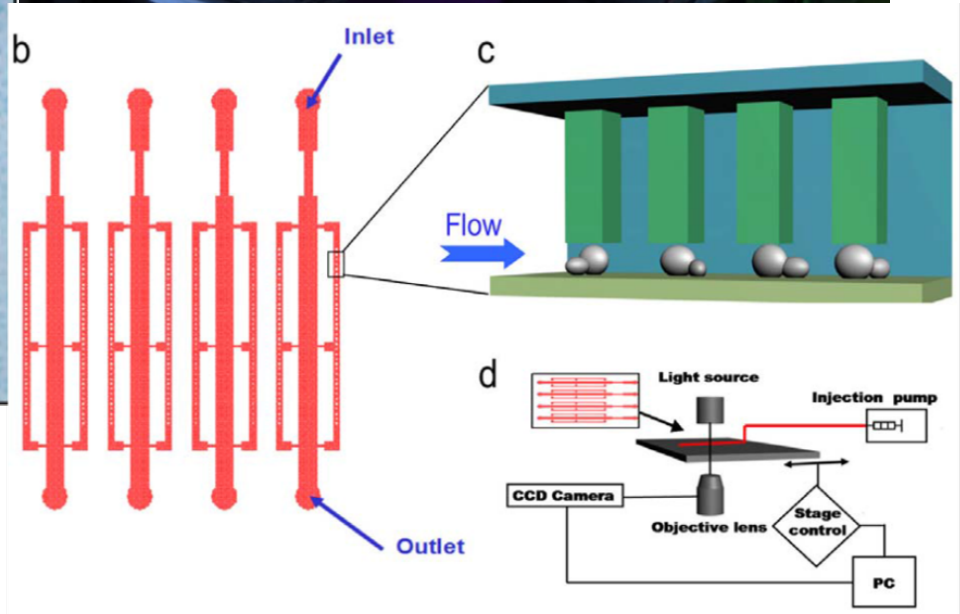
Aging: Just another biological process











Worms and aging genes

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   Susceptibility to disease
   Increasing probability of death
   Loss of resilience to stressors
   Loss of reproduction capacity

3. Operationalize it for studies

   Cell divisions
   Lifespan of a laboratory worm
   Multimorbidity

Mair Lab, Harvard

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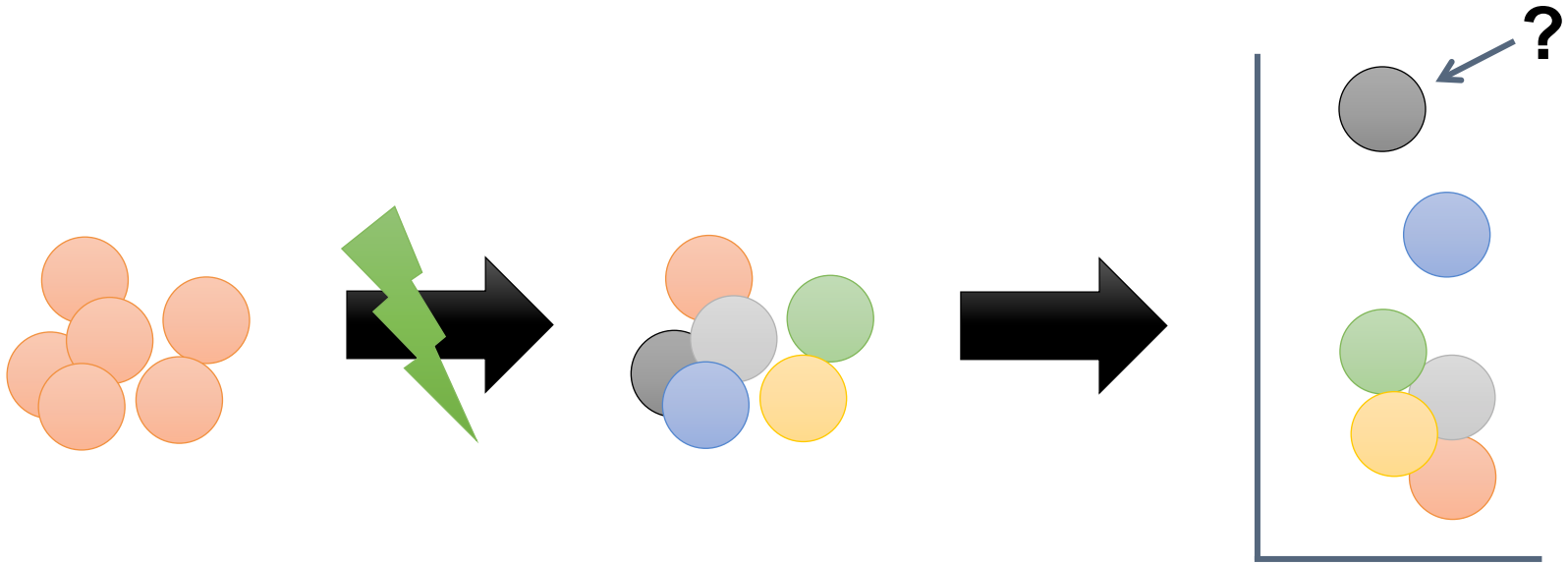
Genetic screens



Normal, identical worms

Create random mutations

Worms with genetic differences

“Assay”: lifespan

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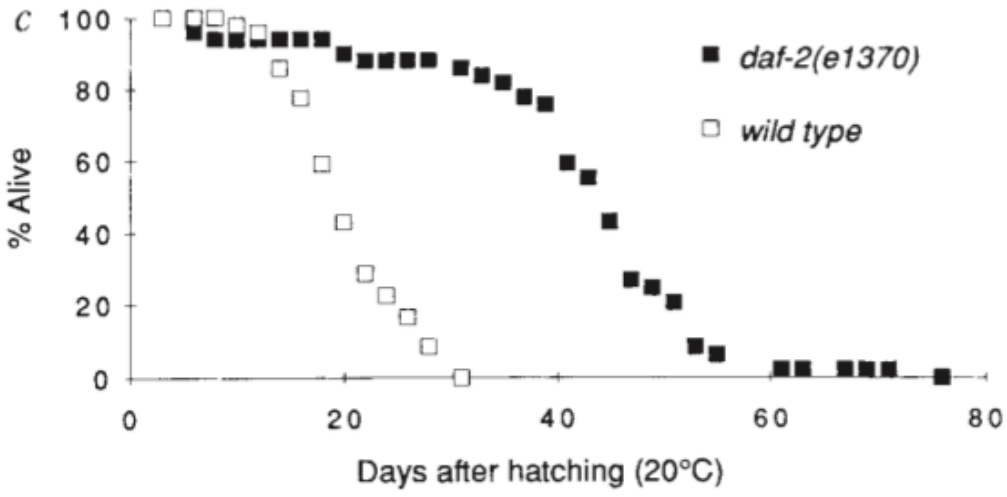
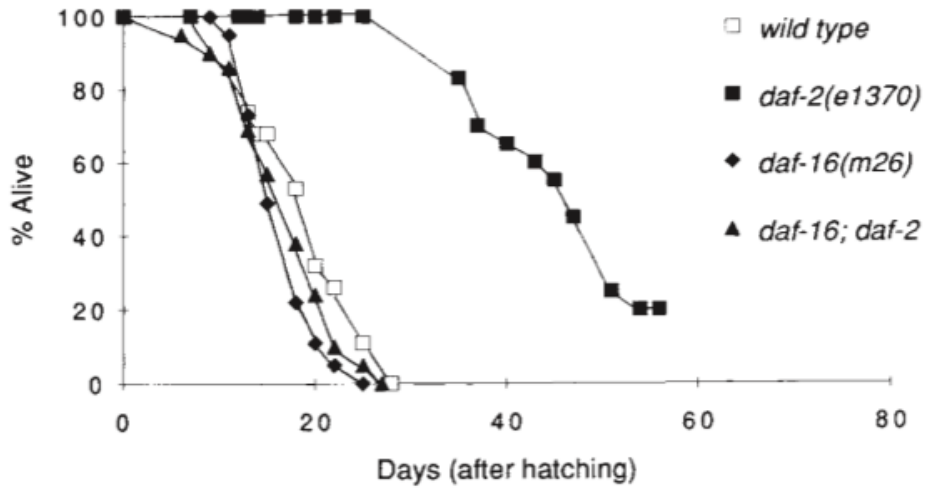
Worms and aging genes





Mutation in the worm version of **insulin** and **growth hormone** pathway = longer life

Mapping entire "**aging pathways**" by seeing how different mutations interact with each other

Cynthia Kenyon, UCSF

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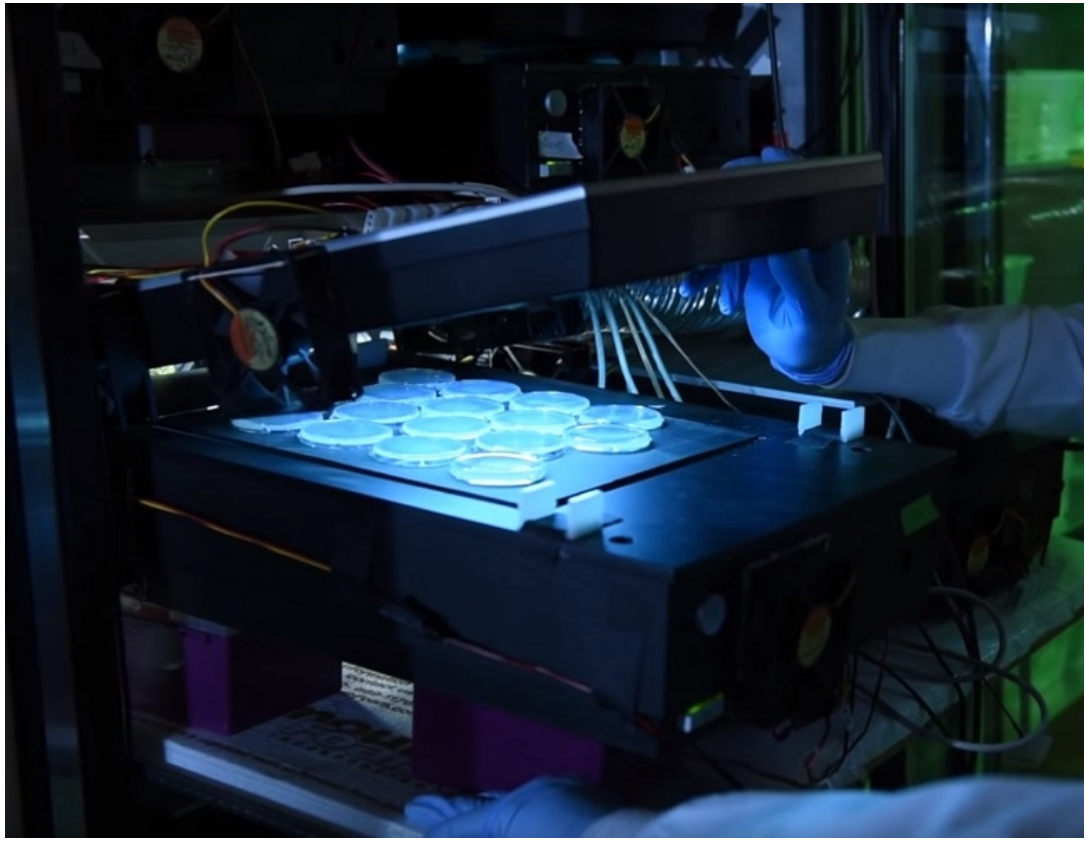
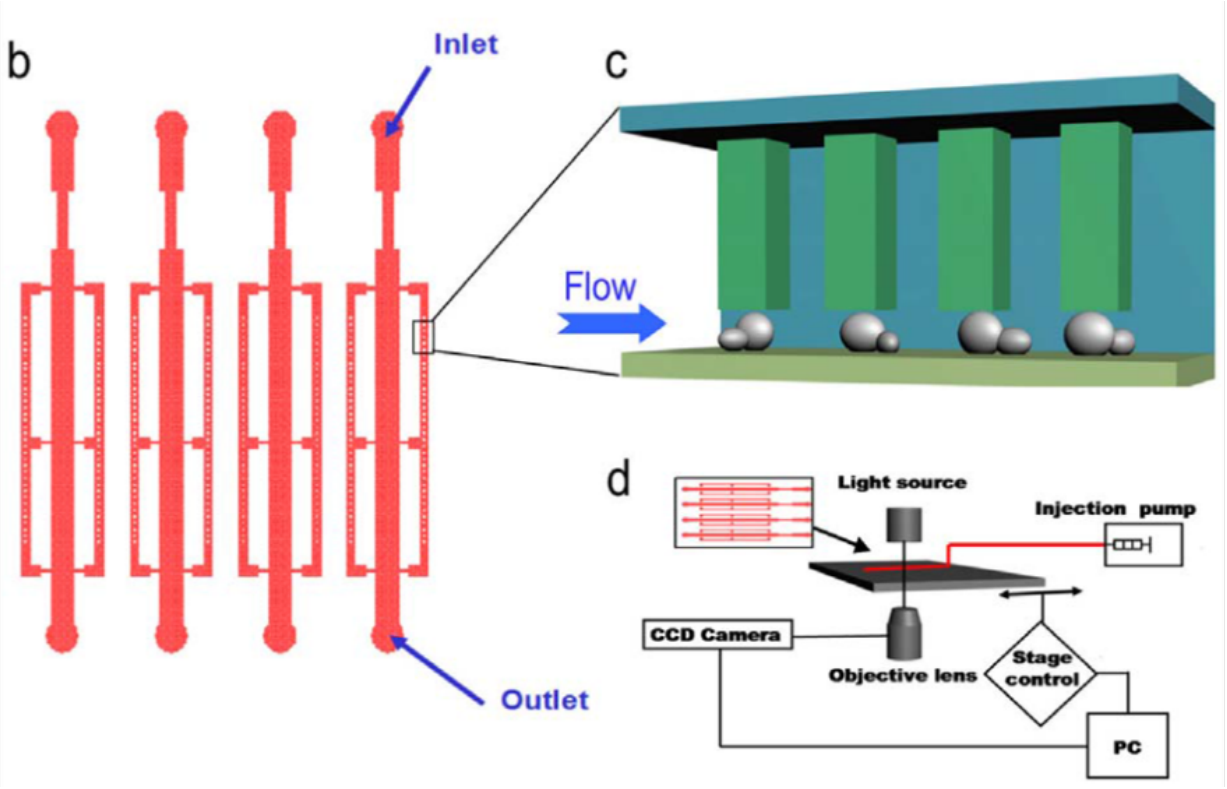
“High throughput” aging science



Scanner-based C. elegans “lifespan machine” with automated data processing



Microfluidic chip and microscopy-based yeast replicative aging assay

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Hallmarks Of Aging…

Lopez-Otin, Cell 2013

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Damage

DNA damage
Protein damage and misfolding
Epigenetic damage
Telomere damage

Consequences

Senescent cells
Stem cell exhaustion
Mitochondrial dysfunction
Chronic inflammation

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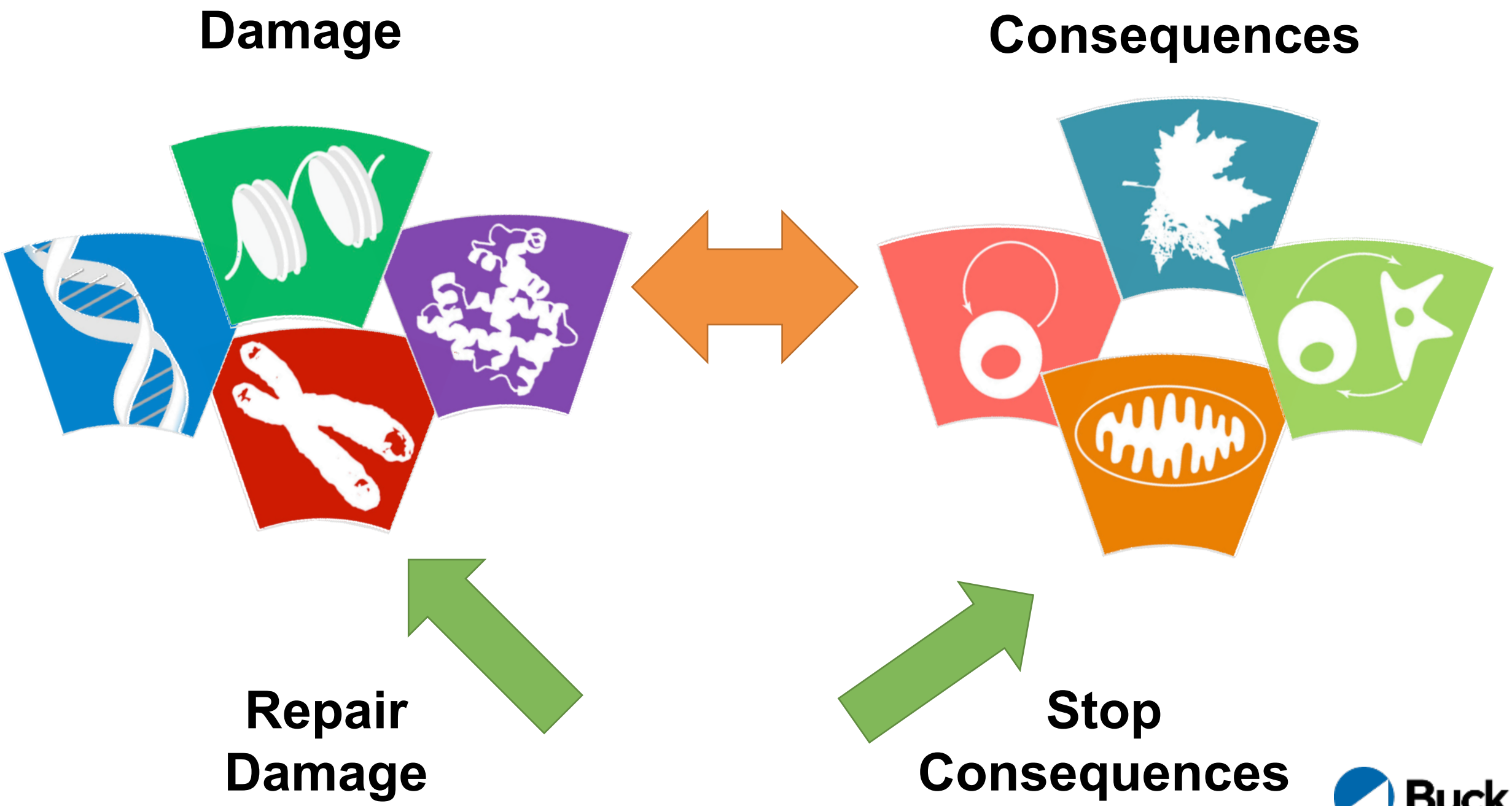
Damage
Consequences
Repair Damage
Stop Consequences
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Metabolic signals and stress response

Less Nutrients/

Me olic

Stress Response

FOXO3
Sirtuins
Autophagy
Mitophagy

DRUGS:
Metformin
Rapamycin
…

Senescent cells and senolytics

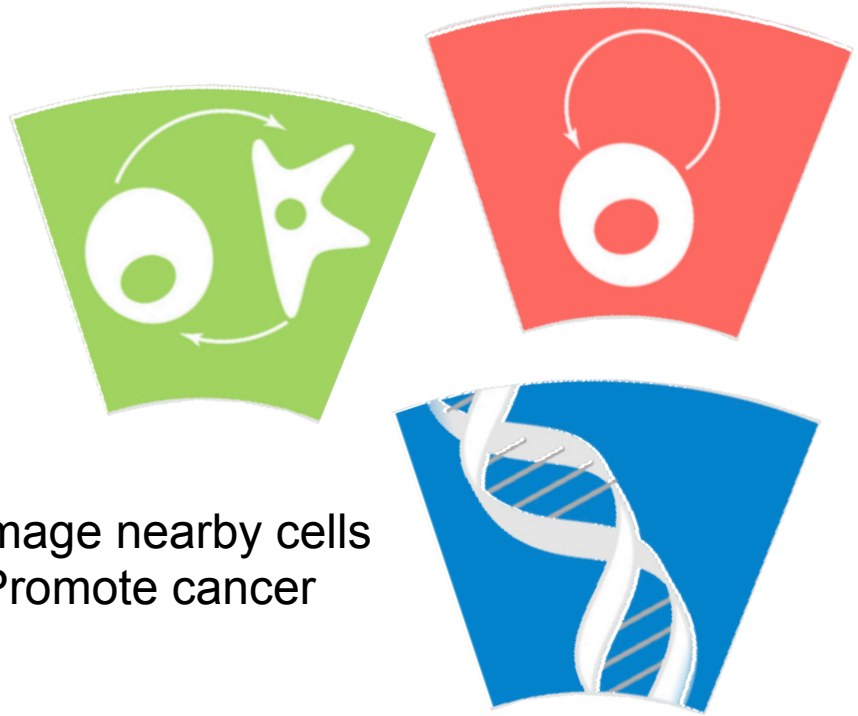
Damage

DNA damage
Short telomeres

Senescence

Stop dividing =
no cancer
“Zombie cell”

Inflammation



Damage nearby cells
Promote cancer

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Senescent cells and senolytics

Damage

DNA damage
Short telomeres

Senescence

Inflammation

Senolytics

(DRUGS)

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Senescent cells and senolytics

Stem Cell
~~Exhaustion~~

New stem cells?

Muscles
Wound healing
Immune system

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Potential Interventions

<u>Metabolic therapies</u>
Metformin
Rapamycin
Acarbose
NAD supplements (NR, NMN)
Sirtuin activators (SRT2104, SRT1720)
Novel TOR inhibitors
CD38 inhibitors
Ketone esters

<u>Senolytics</u>
Navitoclax
Dasatanib
Quercetin
HSP90 inhibitors (17-AAG, 17-DMAG)
Other BCL-activators

<u>Other drugs</u>
Aspirin
17α−estradiol
NDGA
ACEI/ARBs

<u>Blood factors</u>
Myostatin inhibitors

<u>Dietary</u>
Caloric restriction
Protein restriction
Methionine restriction

<u>Procedures</u>
Young mesenchymal stem cell infusion
Young plasma infusion

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Part 1: Aging Biology

Part 2: Clinical Trials

Part 3: Questions

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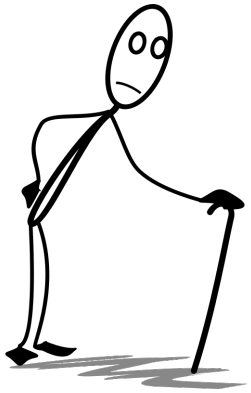
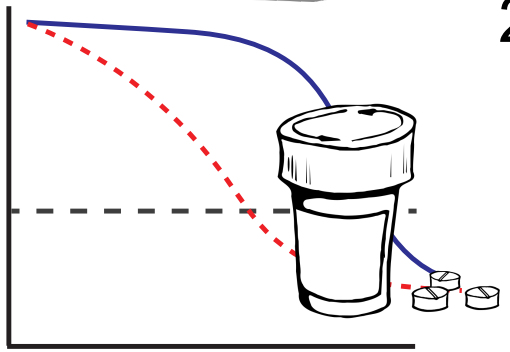
How to study “Aging”





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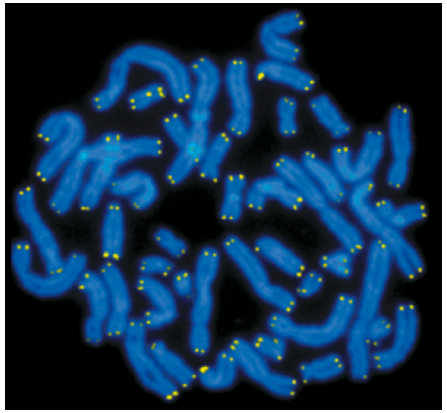

3. Operationalize it for studies

   Cell divisions
   Lifespan
   Multimorbidity

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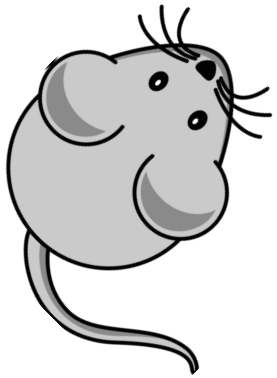
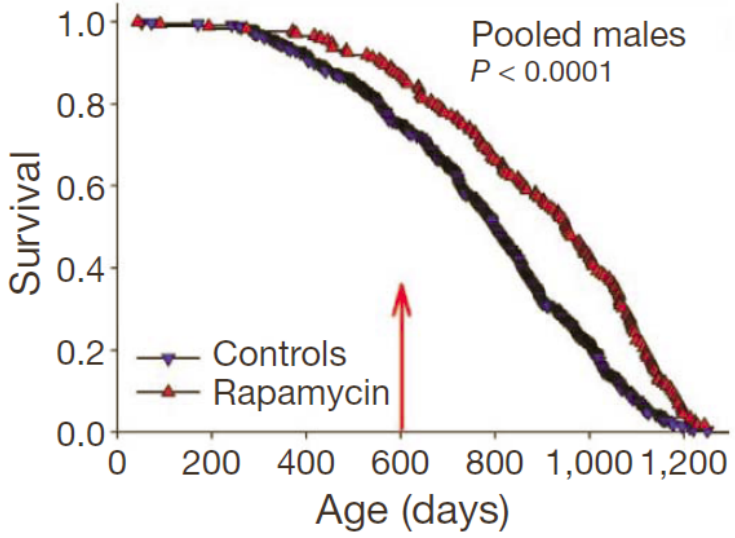
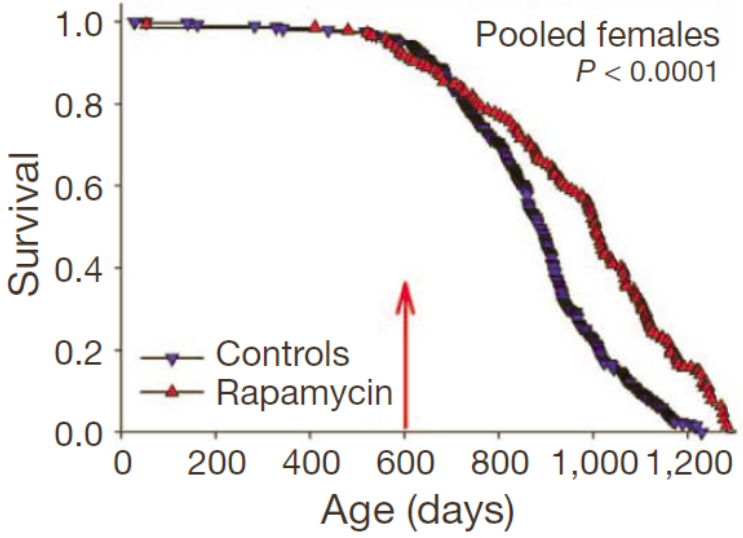
“Pre-clinical trials” of lifespan in laboratory animals

US National Institute on Aging
Interventions Testing Program
Multicenter ”Clinical Trial” for mice

>30 compounds tested/testing
~7 “hits” so far







Harrison, Nature 2009

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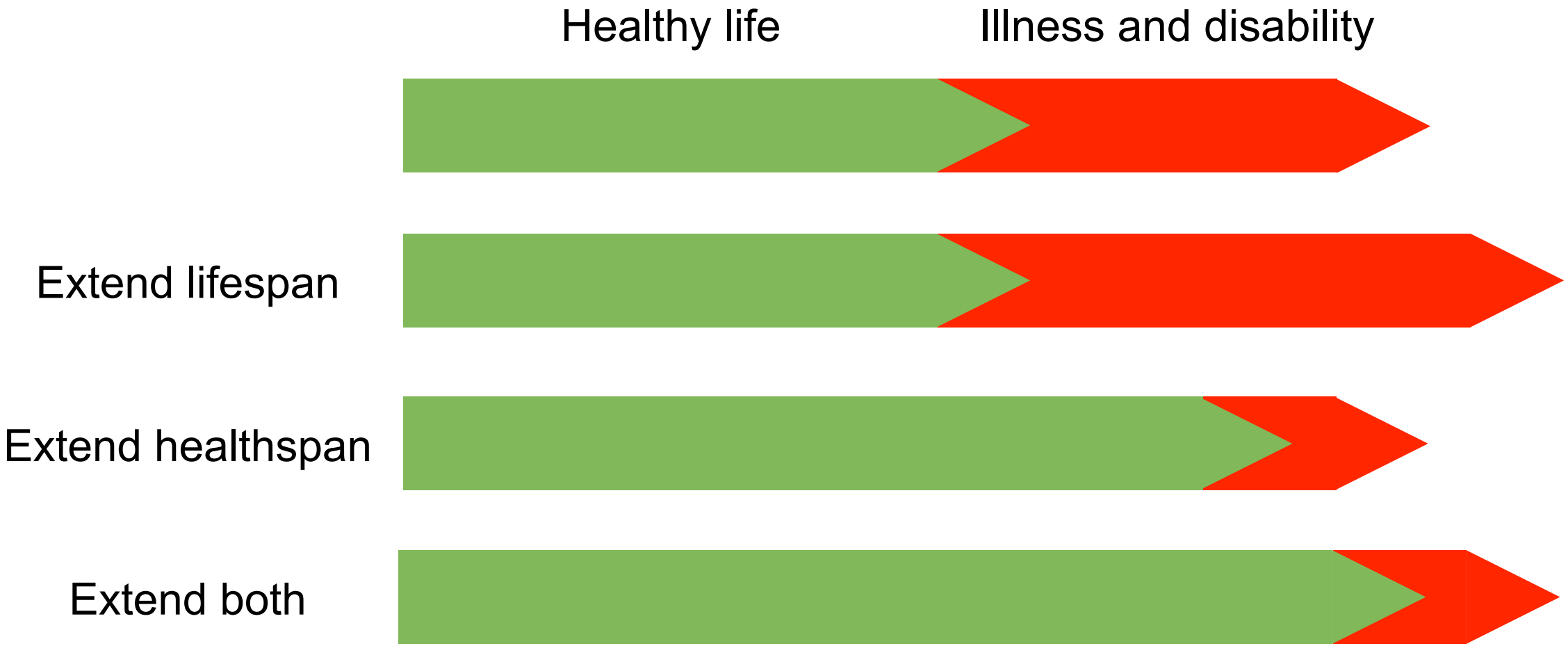
How to test aging interventions in humans?



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How to measure aging in humans?

Healthy life — Illness and disability

Extend healthspan

"Age" is not a number:
Calendar age
versus
Physiological age

(If you've seen one 80 year old
you've seen one 80 year old)

Multimorbidity: chronic diseases

Geriatric Syndromes
- **Frailty**
- **Falls**
- **Functional Decline**
- **Delirium**

Loss of resilience to acute stress

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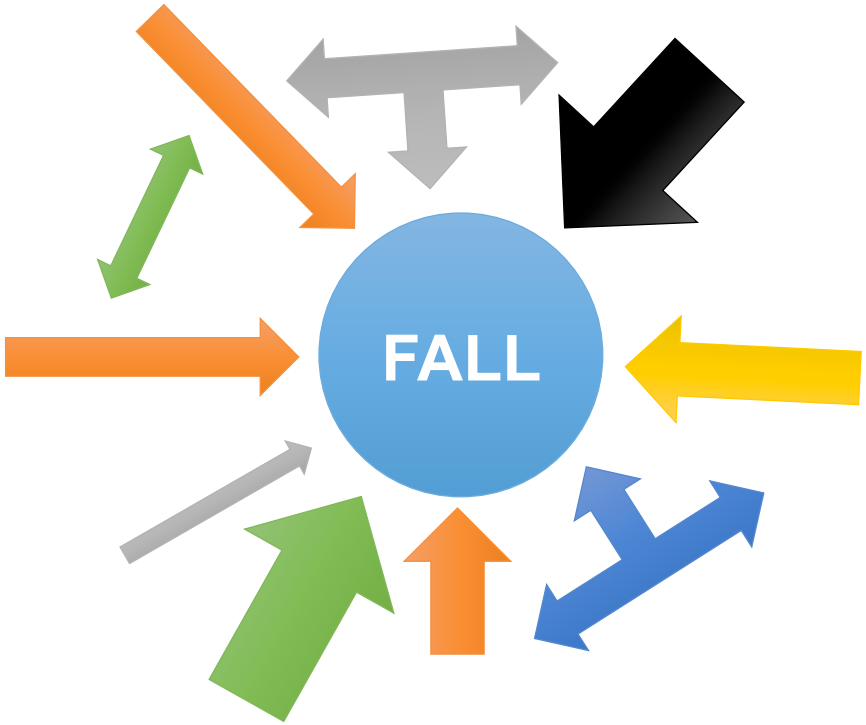
Geriatric syndromes

<u>Geriatric syndrome:</u>
Multifactorial
Multisystem
Age-related
Integrative outcome



Frailty
Falls
Cognitive decline
Mobility decline
Delirium
Chronic wounds
Etc etc…

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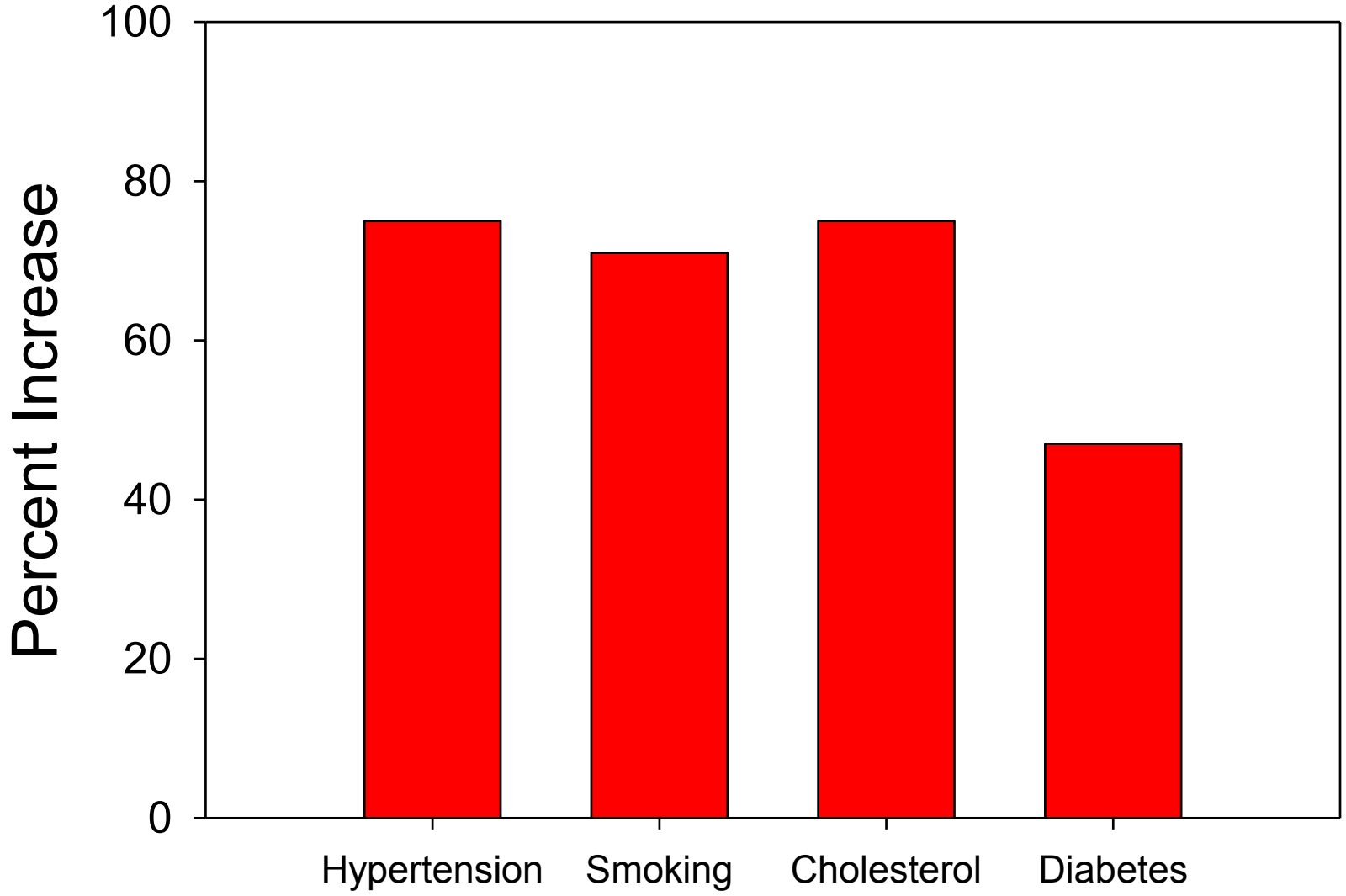
Heart disease risk factors



Steve Austad, University of Alabama

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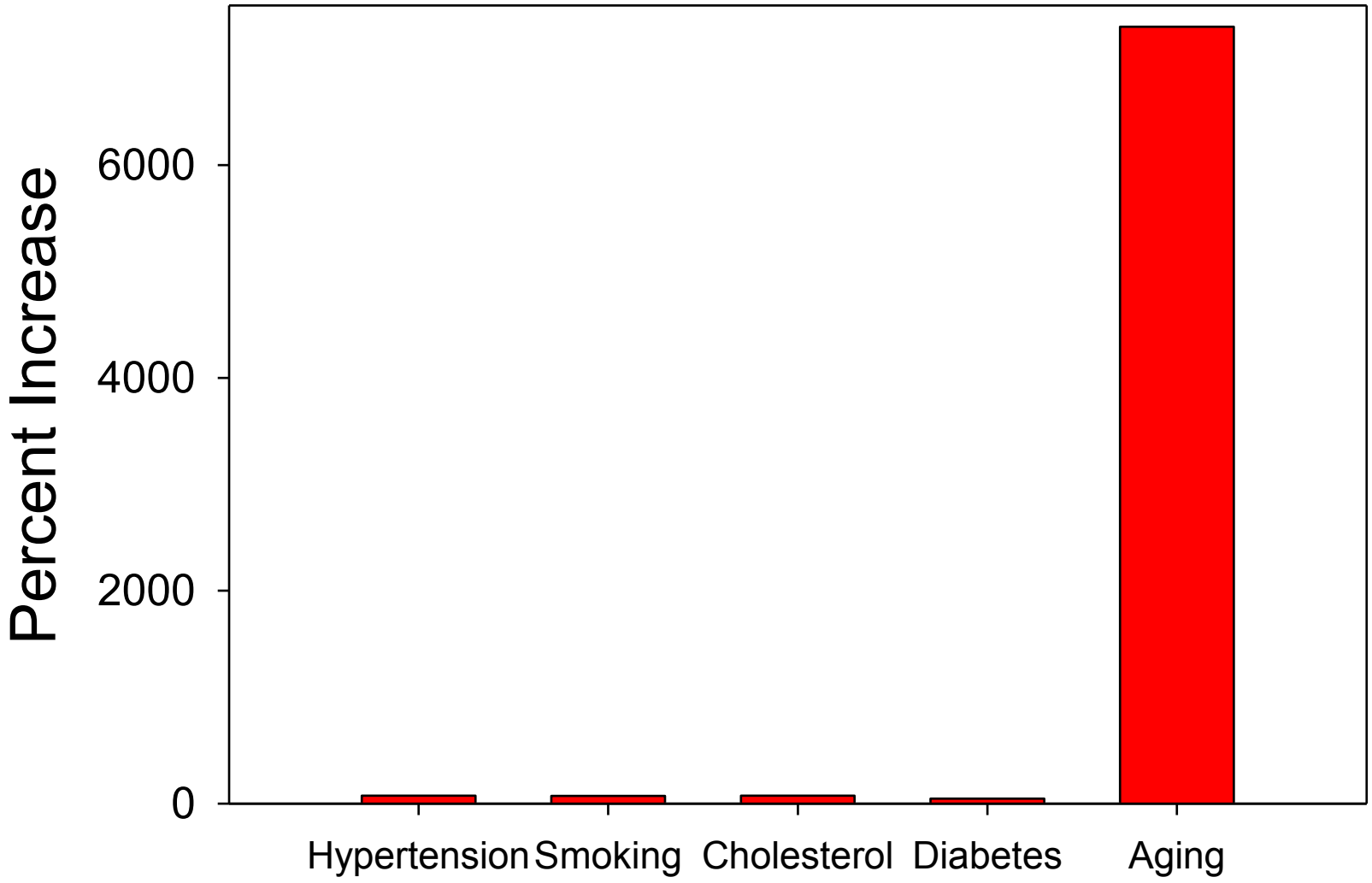
Heart disease risk factors



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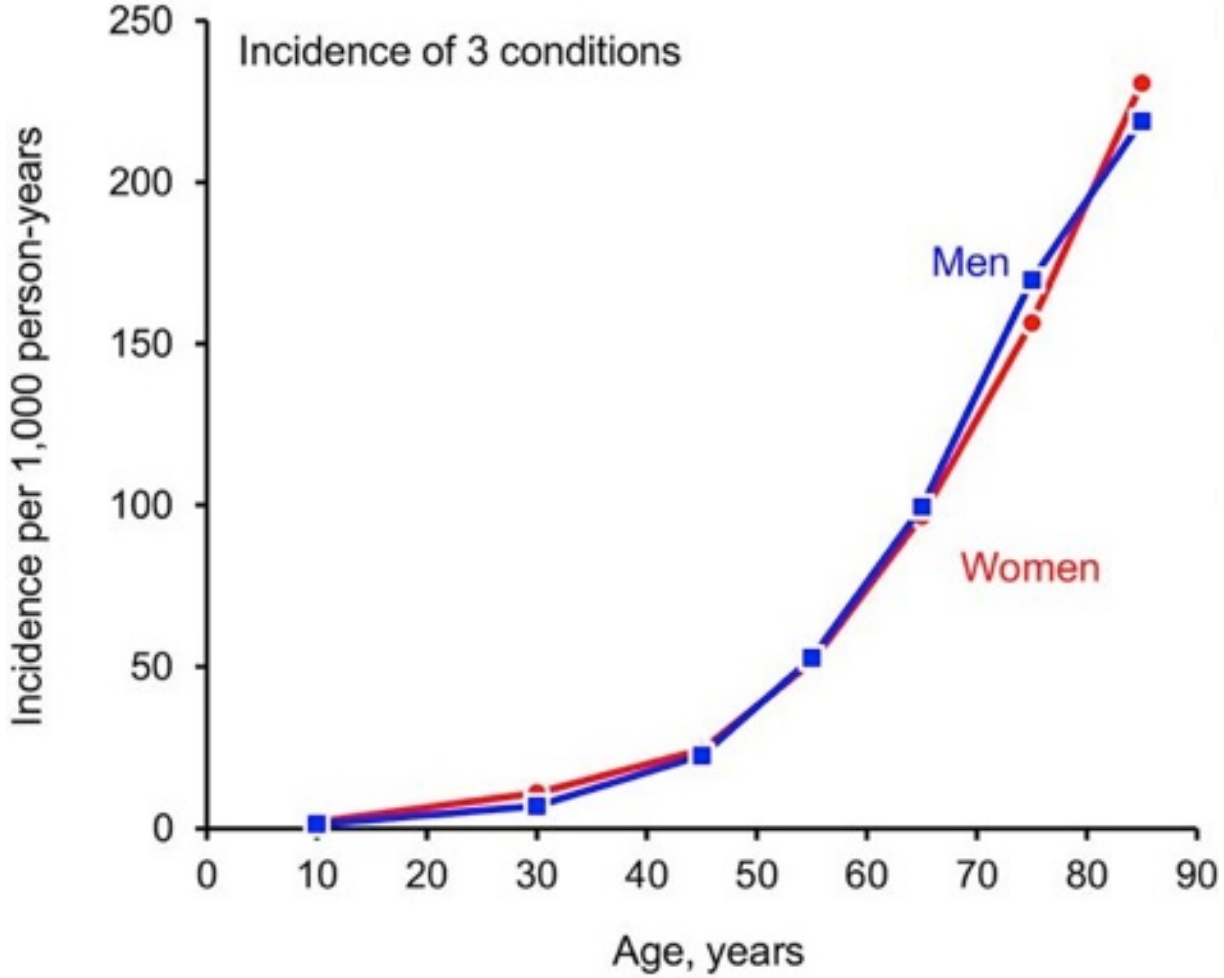
Multimorbidity



Age is a risk for most chronic diseases…

So most chronic diseases don’t happen alone

Rochester Epidemiology Project

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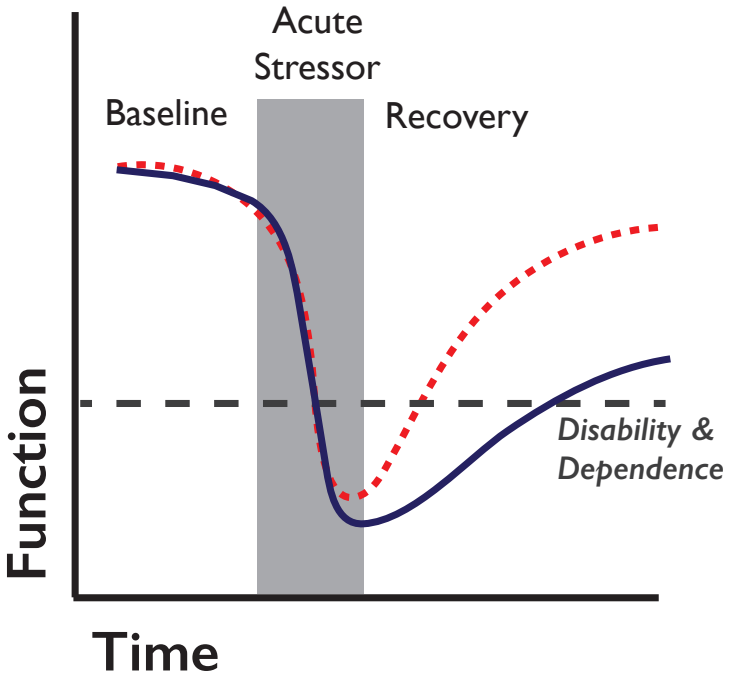
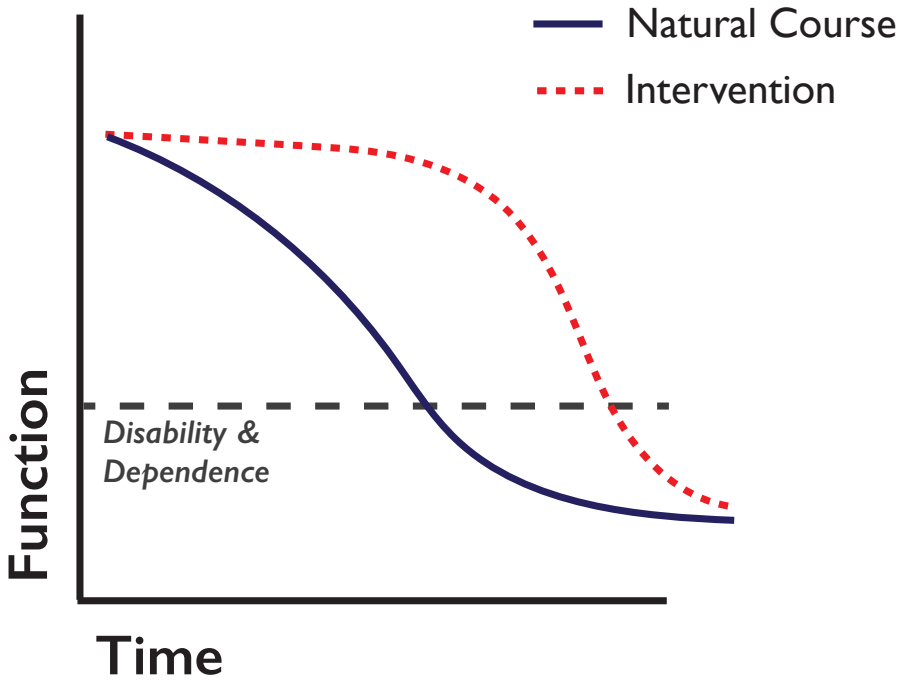
Designing Clinical Trials for “Aging”

Functional Reserve
or “Resilience”



“Healthspan”:
Multimorbidity or
geriatric syndromes



Newman, J Geron 2016

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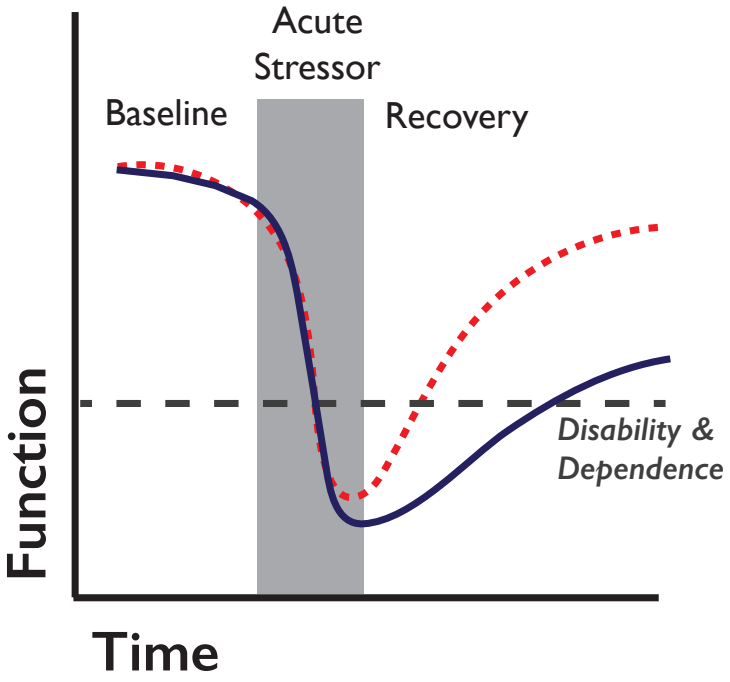
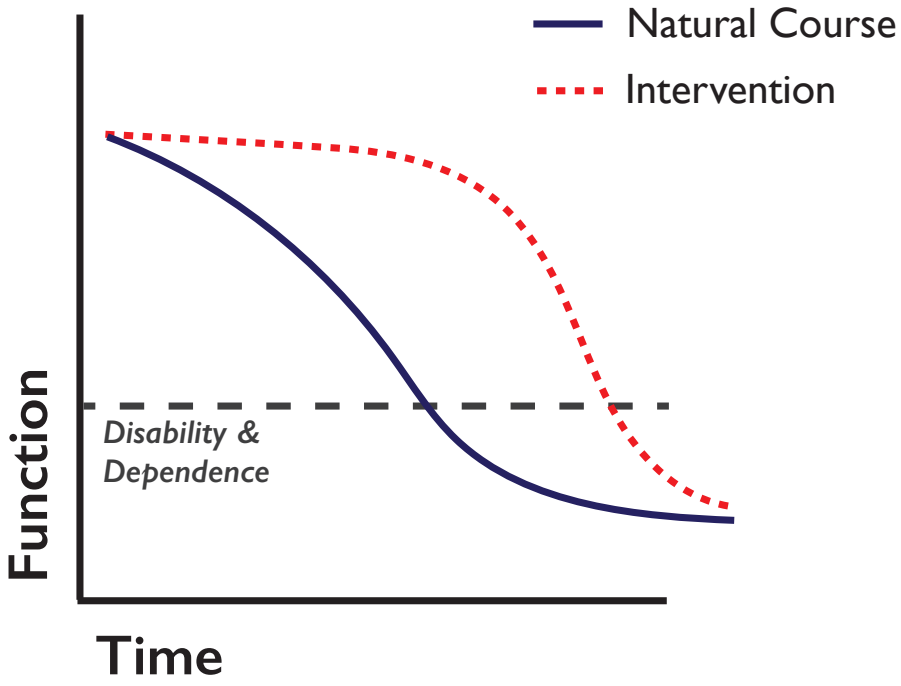
Designing Clinical Trials for “Aging”

Geriatric specialty hospital wards



Exercise for improving frailty



Newman, J Geron 2016

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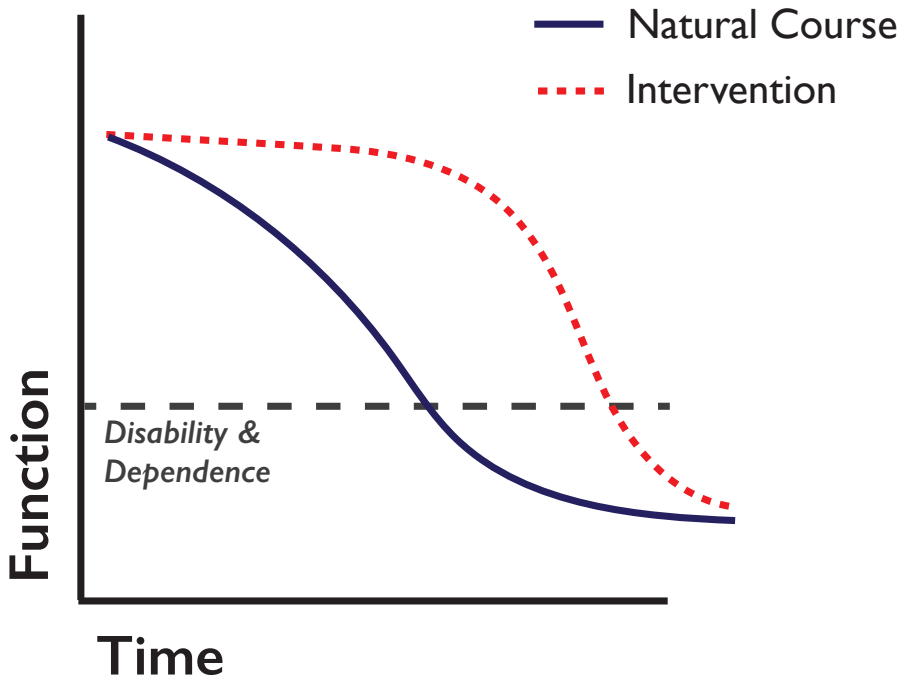
Multimorbidity or Geriatric Syndromes

Rapamycin for preventing respiratory infections in frail elderly
(PureTech/resTORbio)

Metformin to delay the onset of multiple chronic diseases
("TAME: Targeting Aging with Metformin", public consortium)

Young mesenchymal stem cell infusion to treat frailty
(Longeveron, U. Miami)

"Healthspan":
Multimorbidity, function,
or geriatric syndromes



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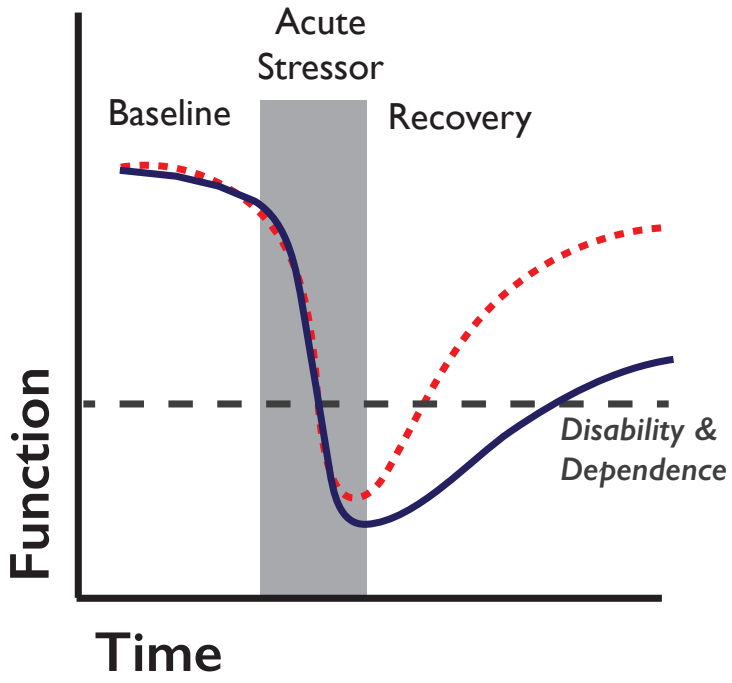
Health stress or hospitalization

Functional Reserve
or “Resilience”



Rapamycin improves influenza vaccine effect
(Novartis, Science Trans Med 2014)

Rapamycin plus cardiac rehabilitation in the elderly
(Mayo Clinic)

Metformin with resistance exercise training in the elderly
(U. Kentucky, U. Alabama)

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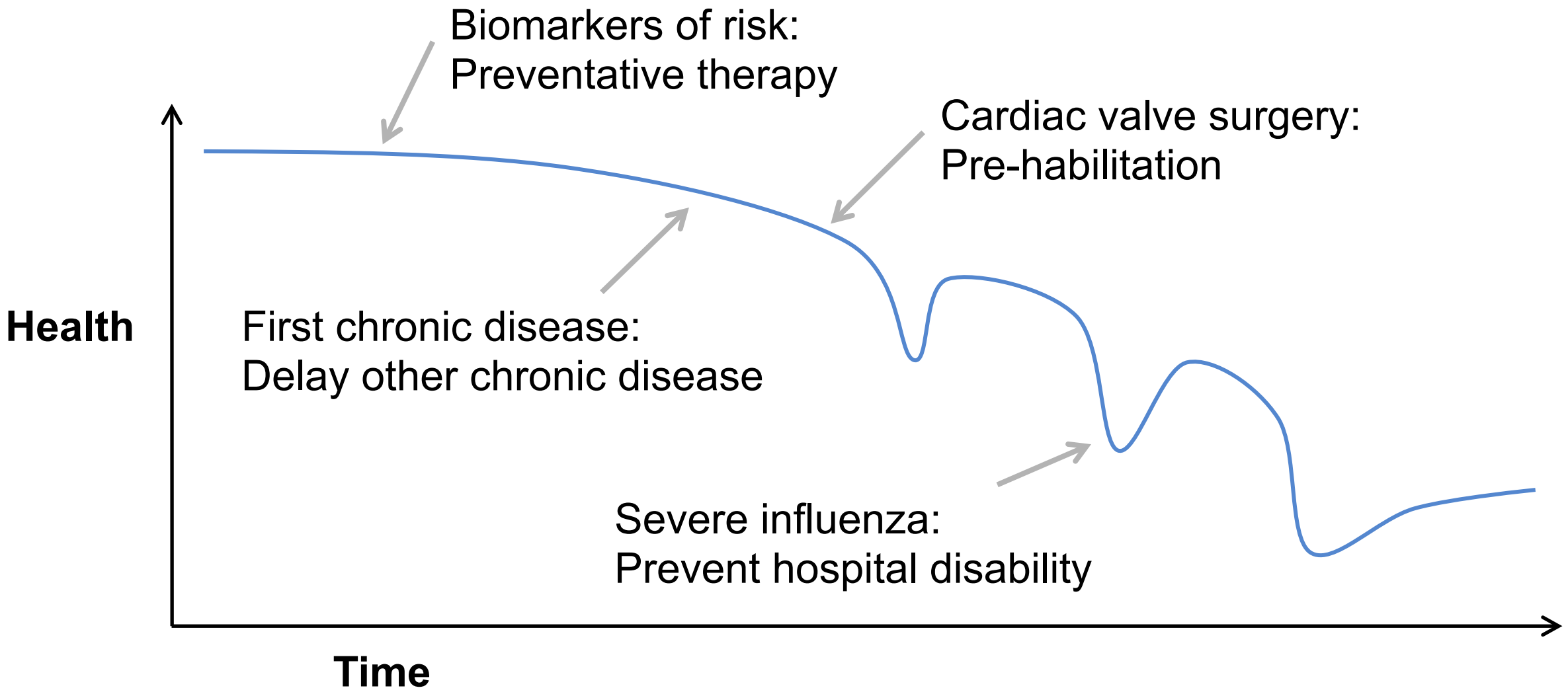
Biomarkers of risk:
Preventative therapy
Cardiac valve surgery:
Pre-habilitation
Health
First chronic disease:
Delay other chronic disease
Severe influenza:
Prevent hospital disability
Time

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Part 1: Aging Biology

Part 2: Clinical Trials

Part 3: Questions

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Aging is universal

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Is ”Aging” a disease?

It happens to everyone!

If not, what does a drug company or regulatory agency do?

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What aspect of aging will clinical trials target?

Do researchers and doctors decide?

Should the broad community have a say?

What do older adults think is important to *them*?

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Large clinical trials of frail, vulnerable, elderly people?

First to harm, last to help…

We test cancer drugs in patients with cancer…

We need more clinical trials in the elderly anyway!

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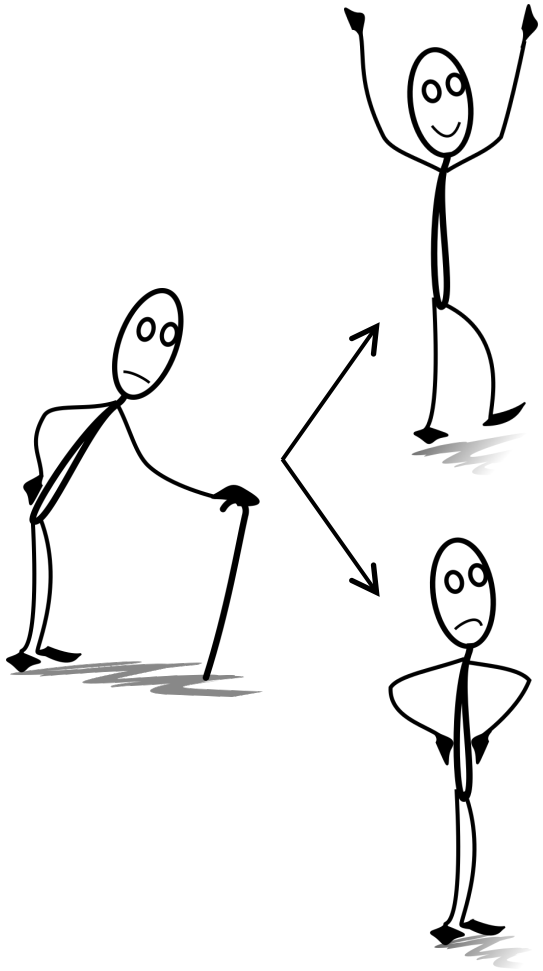
Who will get these treatments?

Everyone, right? Right?

What if it's expensive?

What if it's rare?



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Expensive Treatments

Expensive by choice: Novel senolytics

Hepatitis C cures

Expensive by design: Aging-factor blocking antibodies

Antibody-based drugs

Expensive by technology: Autologous organoids or stem cells

CAR-T, Dialysis

Expensive by scarcity: Young blood/cell infusion

Transfusion, organ transplant

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Aside: Frankenstein medicine

“Replacement parts” approach to medicine does not work

Transplants, dialysis, LVADs, etc etc – it’s never just one thing. The whole person is old and frail.

What if aging therapies change that?

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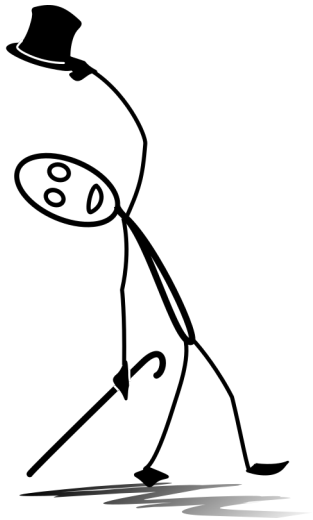
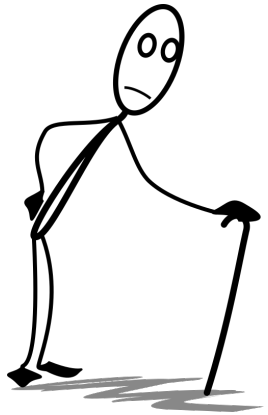
Who will benefit?

Everyone, right? Right?

Fancy heath care can exacerbate disparities



But it's easier to fix what's broken – who is most affected by aging now?



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Will aging therapies exacerbate or reduce health disparities?

Rich already live longer – less room to improve

Poor and disadvantaged have vicious cycle of health problems, accelerated aging, and geriatric syndromes

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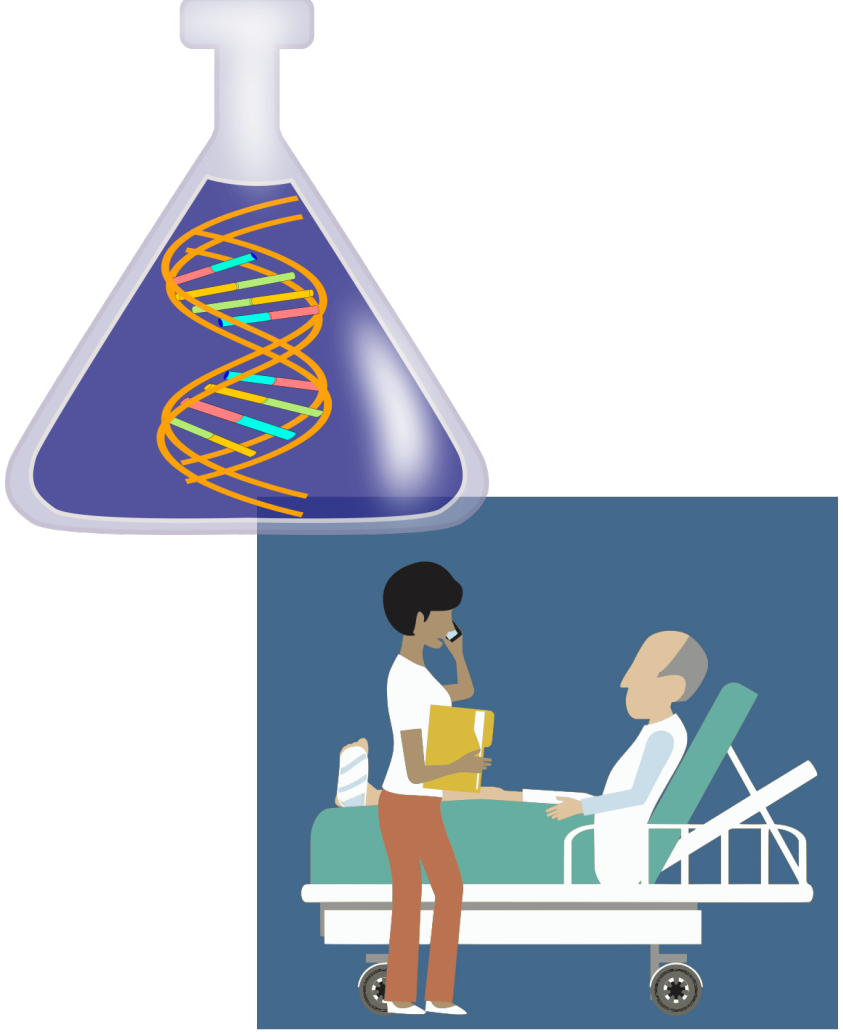
Aging biology is here

Clinical trials are happening

What do we do from here?



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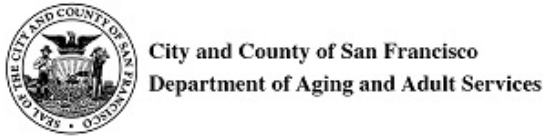
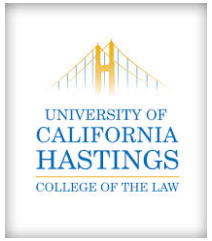
Optimizing Aging Collaborative at UCSF





For more information, visit us online at OptimizingAging.com
or email us at OAC@ucsf.edu.

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