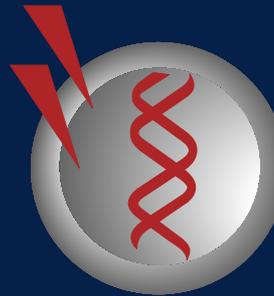




Division of  
Geriatrics  
Department of Medicine



GLADSTONE  
INSTITUTE OF  
VIROLOGY AND  
IMMUNOLOGY

# Strategies and Challenges in Human Clinical Trials Targeting Aging

John Newman, MD, PhD  
UCSF and Gladstone Institutes

[newman@ucsf.edu](mailto:newman@ucsf.edu)  
[@GeriSciDoc](https://twitter.com/GeriSciDoc)

# The Geroscience Hypothesis

Targeting **fundamental aging processes** might delay, prevent, alleviate, or reverse a **wide range** of diseases and conditions for which age is the primary non-modifiable risk factor.

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Special Issue: Moving Geroscience into Uncharted Waters: Perspective

## **Strategies and Challenges in Clinical Trials Targeting Human Aging**

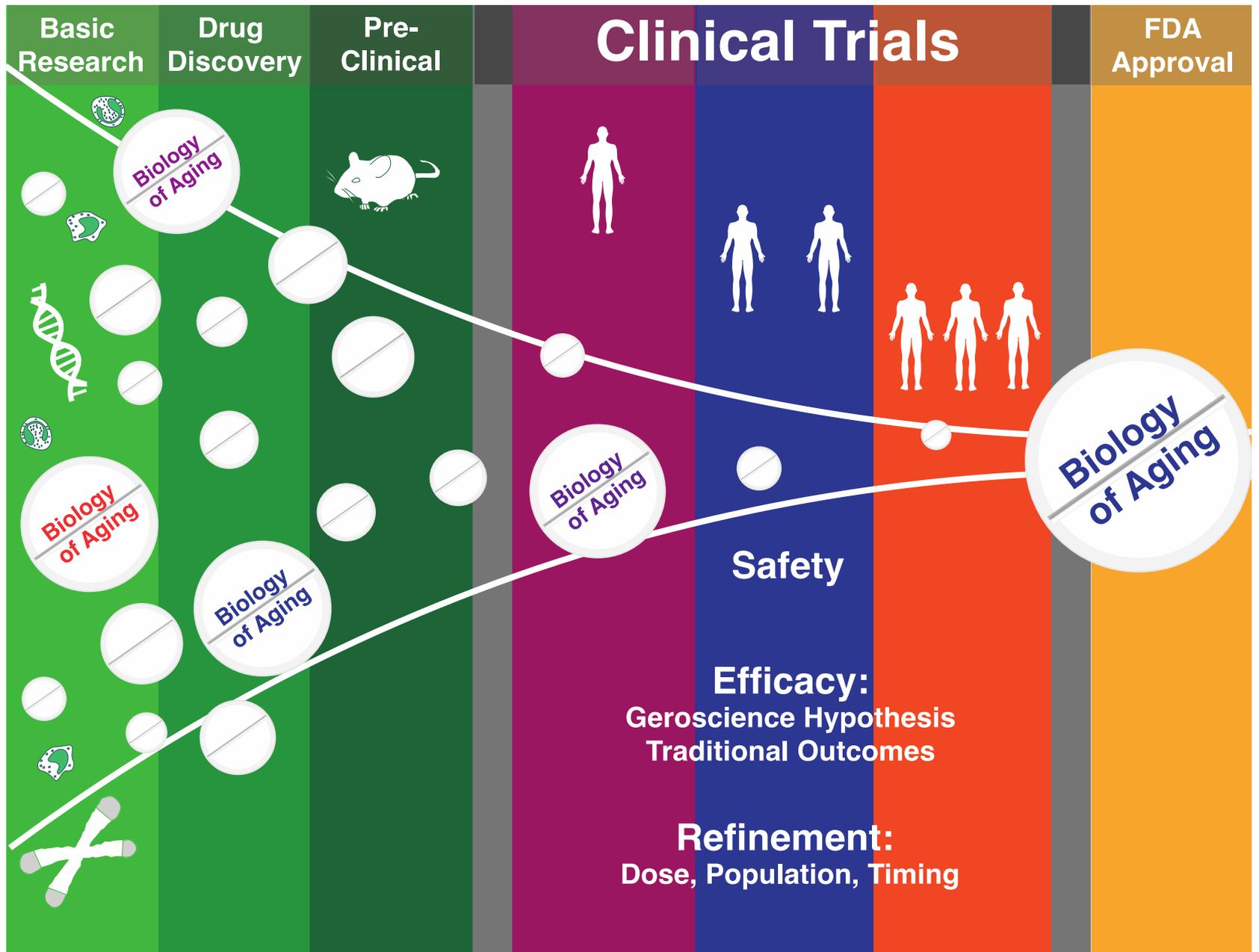
**John C. Newman,<sup>1,\*</sup> Sofiya Milman,<sup>2,3,\*</sup> Shahrukh K. Hashmi,<sup>4</sup> Steve N. Austad,<sup>5</sup> James L. Kirkland,<sup>6</sup> Jeffrey B. Halter<sup>7</sup>, and Nir Barzilai<sup>2,3</sup>**

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Special Issue: Moving Geroscience into Uncharted Waters: Perspective

## **Frameworks for Proof-of-Concept Clinical Trials of Interventions That Target Fundamental Aging Processes**

**Jamie Justice,<sup>1,\*</sup> Jordan D. Miller,<sup>2,3,4,\*</sup> John C. Newman,<sup>5,\*</sup> Shahrukh K. Hashmi,<sup>6</sup> Jeffrey Halter,<sup>7</sup> Steve N. Austad,<sup>8</sup> Nir Barzilai,<sup>9,10</sup> and James L. Kirkland<sup>3,4</sup>**



**Think Big**  
**Study Patients**  
**New Tools**  
**Easy Mode**

# Think big



Do you want to lower cholesterol or do you want to change people's lives?

# Outcomes for aging interventions

**Age-related Diseases:**  
T2DM, CAD, CKD,  
Alzheimer's, Parkinson's



**Physiological Age**

**Age-related Changes:**  
Muscle loss, kidney function



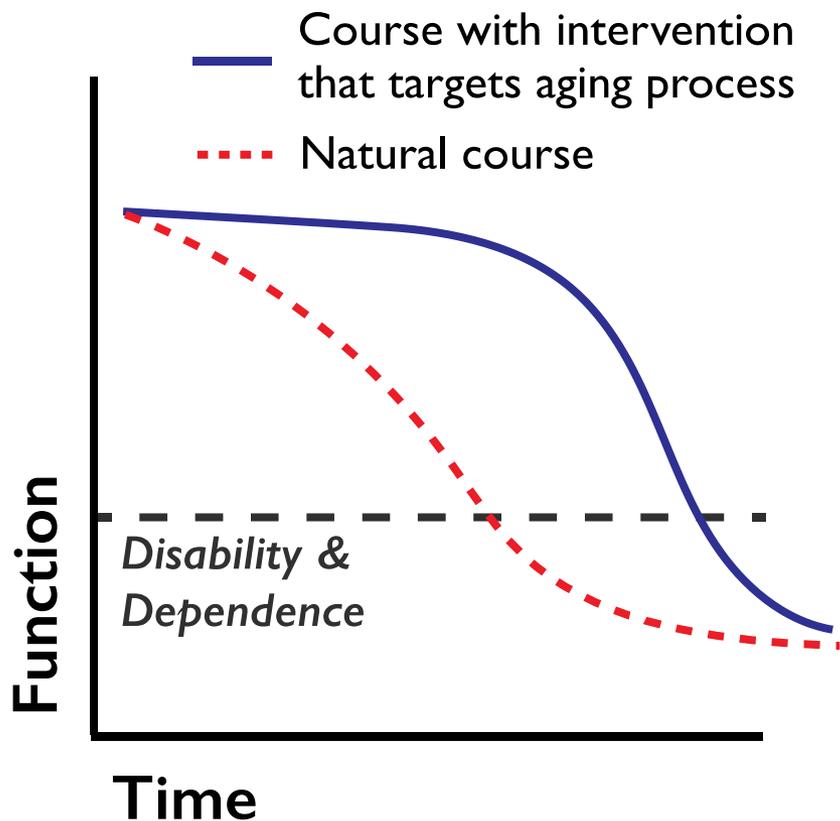
**Functional outcomes**

**Geriatric syndromes**

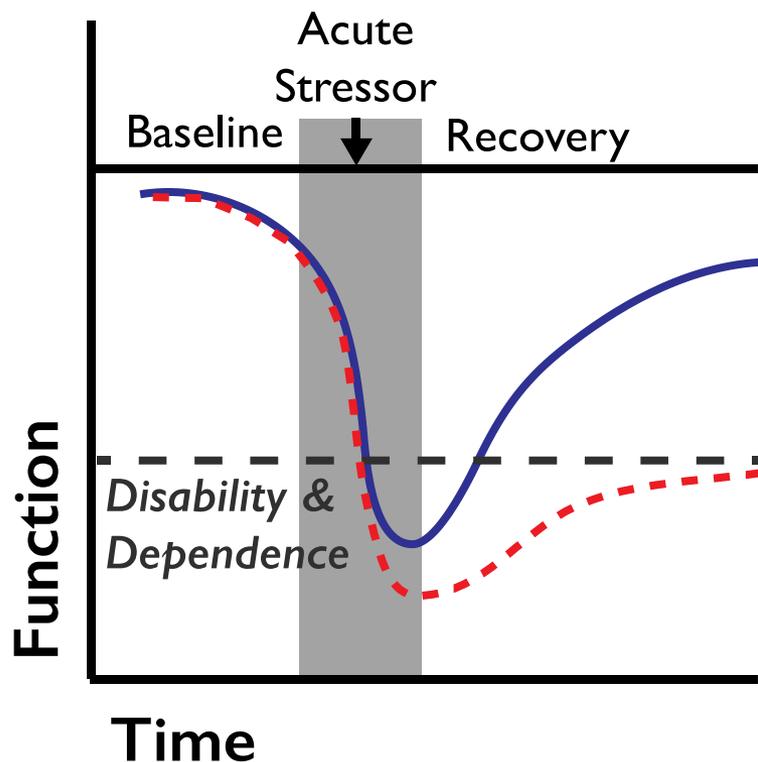
**Mortality**

# Scenarios for Clinical Trials of Aging

## A. Extending Healthspan



## B. Enhancing Resilience



# Scenarios for Clinical Trials of Aging

## A. Extending Healthspan

Slow/prevent the progressive decline with age

Long-term studies: years?

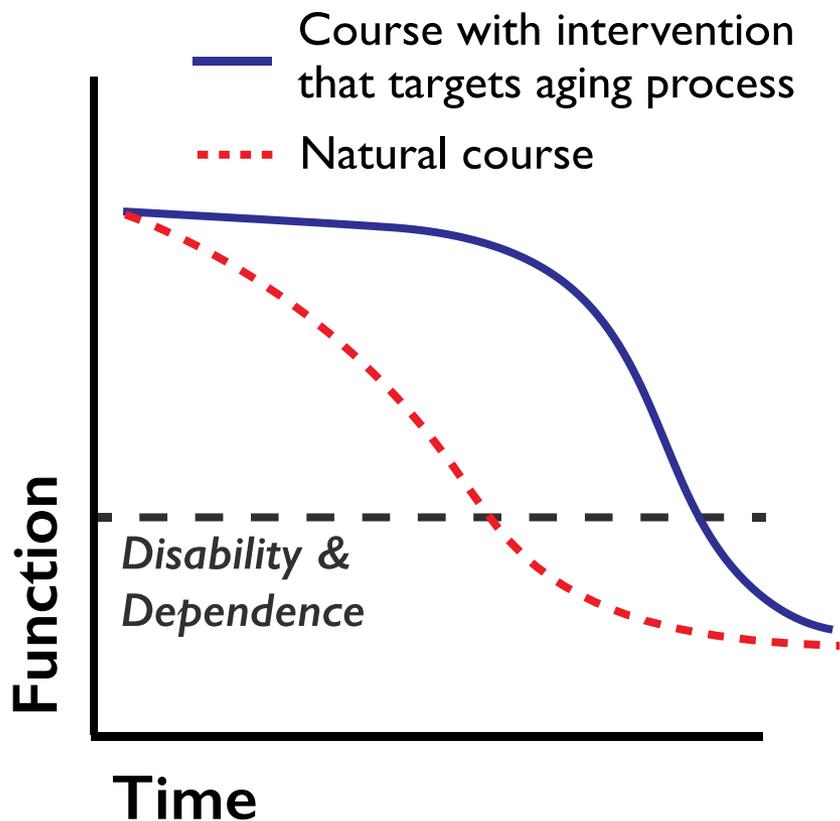
Global outcomes representative of aging:

Multimorbidity

Geriatric syndromes

Functional decline

Multisystem effects



# Scenarios for Clinical Trials of Aging

Improve the response to a stressor

May be short, with longer follow-up

Intensity of stressor:

Immunization

Wound healing

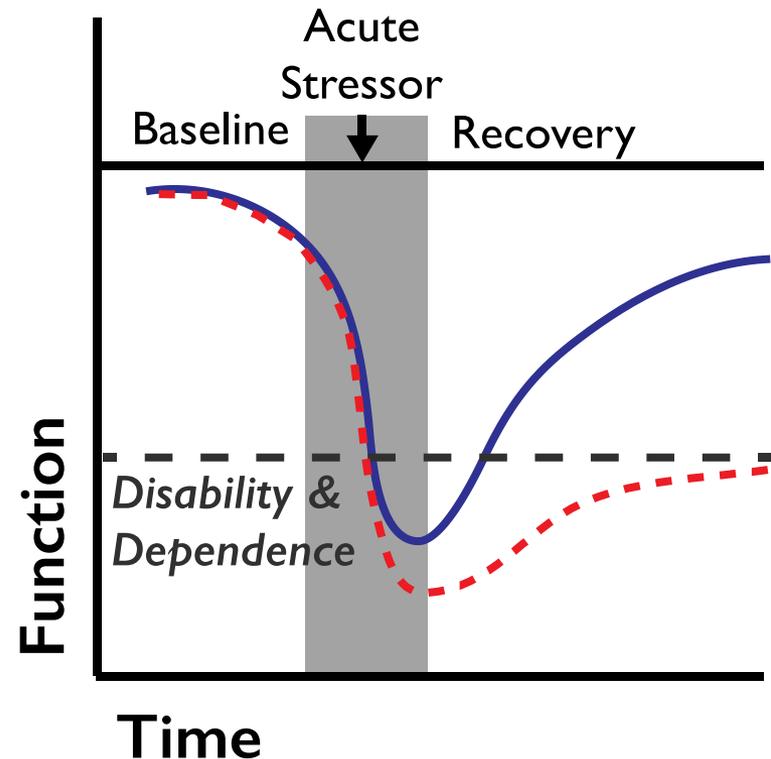
Surgery/Chemotherapy

Planned vs. unplanned stressor

Pre-, peri-, or post-stressor intervention

Primary outcome related to the stressor, but  
global secondary outcomes

## B. Enhancing Resilience



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# Don't Study Spherical Cows



# Don't Study Spherical Cows



# Study the patients you want to treat



*A real-life, non-spherical older adult who strongly values her independence*

**Embrace heterogeneity!**

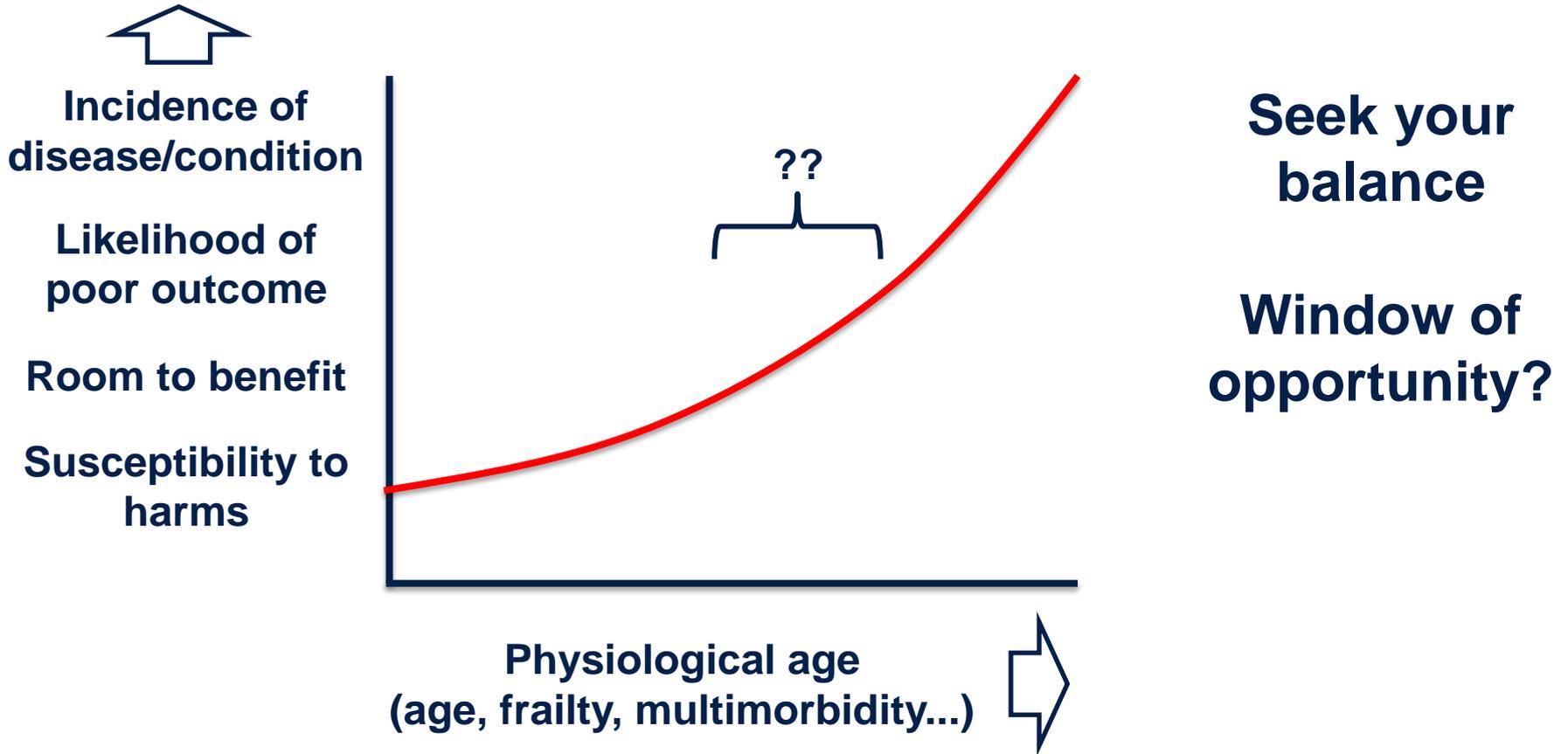
**Many elders are...old**

**Many elders are frail and/or have multiple chronic diseases**

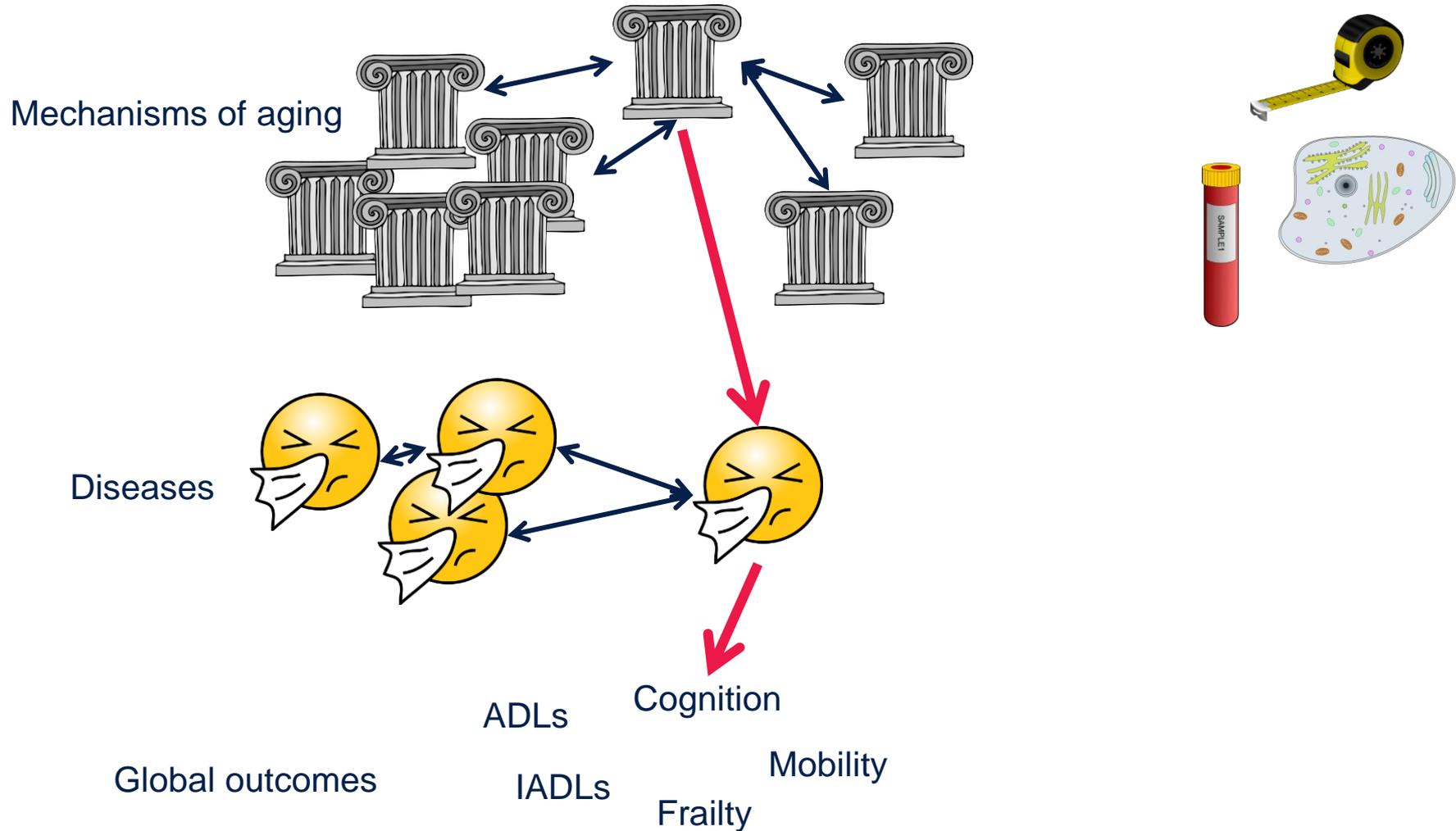
**Age-related diseases occur in the context of *aging***

**Age-related diseases occur in the context of *other age-related diseases***

# Population Selection



# Samples, biomarkers, outcomes



# Outcomes

## How to “measure” aging?

Accumulation of diseases, syndromes, conditions

Decline in daily function: ADLs, IADLs, care settings

Decline in physiological function: gait speed, grip strength, etc.

**Healthspan trials:** Broad aging outcomes, but could some of these be added on to a trial targeting one specific disease/condition?

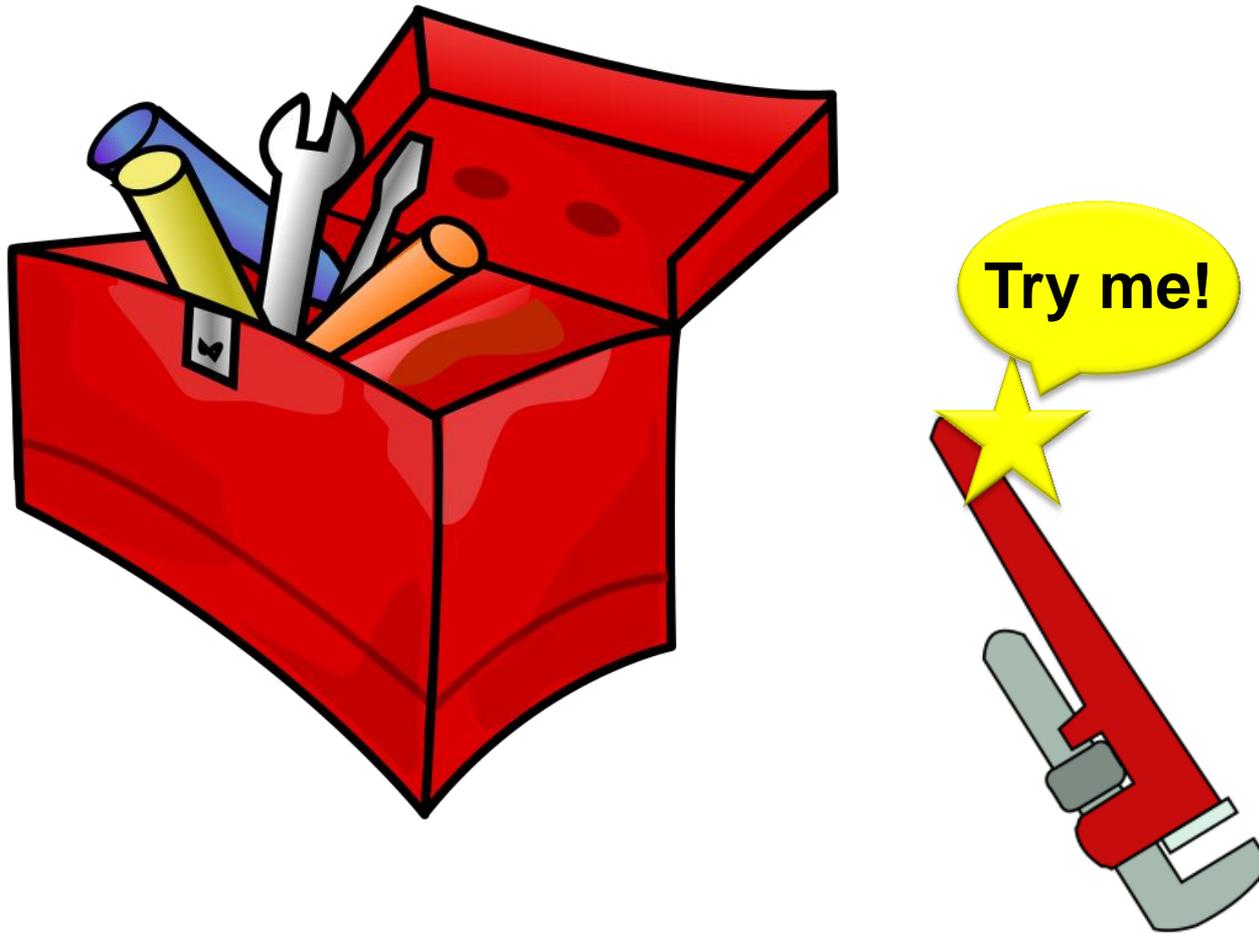
**Resilience trials:** Primary outcome is specific to stress, but should collect broad aging outcomes as well.

**Any trial involving older adults:** Where appropriate, could expand utility and extend results by collecting outcomes and samples broadly relevant to aging

- Longitudinal data collection as a salve for heterogeneity
- Long-term, low-touch follow-up could be very informative
- Development of validated biomarkers is an area for active investigation

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# New tools for you?



# Interventions

Drug	FDA	Current Indication	Safety (adverse reactions)	Effect on Other Age-Related Conditions
Metformin	✓	T2DM	+++ (diarrhea and GI upset)	Reduced risk of CVD, cancer, and dementia
Acarbose	✓	T2DM	+++ (flatulence and diarrhea)	Reduced risk of CVD and hypertension
Resveratrol/sirtuins <sup>a</sup>		None	Limited data	No major studies
Rapamycin/rapalogs <sup>b</sup>	✓	Transplant, cancers <sup>c</sup>	+ (hyperglycemia and oral ulcers)	Improved response to flu vaccine
ACEi/ARB	✓	Cardiovascular <sup>c</sup>	++ (hypotension, hyperkalemia, and renal injury)	Reduced risk of cancer, cognitive decline, and dementia
Aspirin/salicylic acid <sup>a</sup>	✓	Many <sup>c</sup>	++ (bleeding and GI ulcers)	Reduced risk of CVD and cancer
17- $\alpha$ -Estradiol		Alopecia (Europe)	Limited data	No major studies

Dozens of drugs and other interventions are now known to extend healthspan and longevity in rodents. Several of these drugs are already FDA-approved and have human data suggestive of broad effects on aging.

# Interventions

**Safety:** New drugs, and many approved drugs, will require safety testing in the targeted population.

**No panaceas:** Select drugs based on proposed mechanism. Not all drugs are likely to be helpful in all circumstances.

**Fit to study:** Risk of adverse effects and intensity of therapy should be proportionate to the duration and outcomes of the study.

**Combinations:** Multifactorial interventions may prove superior.

**Standard of care:** Leverage existing programs to provide infrastructure as well as comparisons (e.g. ACE units, Prehab clinics).

# Outcomes

## Regulatory agencies:

“Aging” is not an FDA indication

Registration indication is critical for new drugs, and preferable for repurposed drugs

Geroscience hypothesis: drugs will affect multiple diseases/conditions

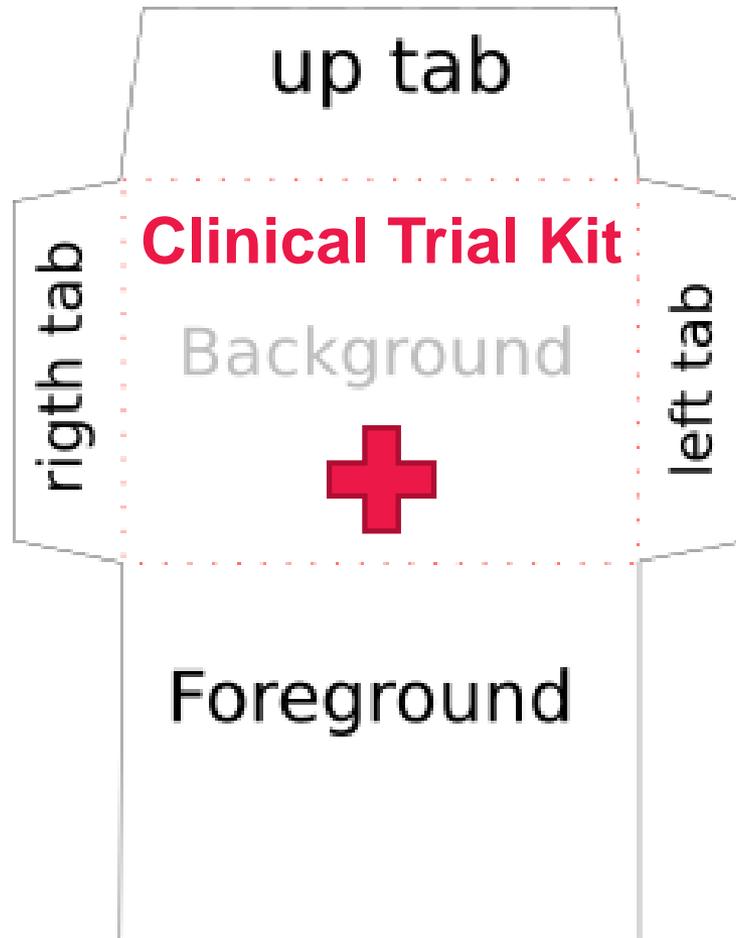
The most impactful aspects of aging involve multiple pathophysiologies

Solution: composite of existing outcomes, e.g. multiple diseases

Solution: Build evidence for adopting syndromes of aging as indications  
Multimorbidity, frailty, ADL/IADL functional decline, delirium  
immobility, cognitive decline, etc.

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# Easy Mode



# Accelerating Progress

## Identifying new interventions:

- systematic expert review of literature/libraries
- standardized pre-clinical screening protocols
- partnering with e.g. NCATS Drug Repurposing Program

## Shared library of templates:

- trial designs, IND applications, IRB proposals, DSMB designs
- all adapted to older adults and outcomes related to aging

## Standardized, modular outcome toolkit:

- potentially applicable to ALL trials involving older adults
- physiological, functional, molecular measures
- natural history data needed!

## National geroscience biobank

- diverse, uniquely enriched for multimorbidity, frailty, elderly
- helpful to ALL investigators studying an age-related disease or a disease in older adults

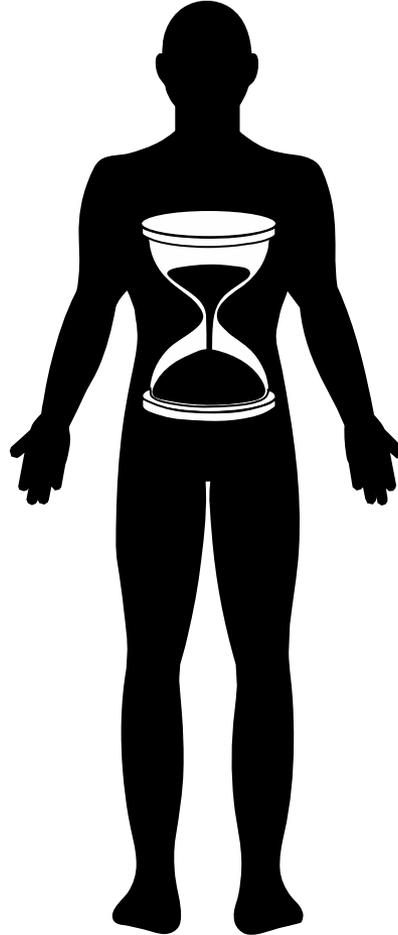
# **Geroscience Network for Aging-Related Proof of Concept Clinical Trials**

**Expert Panel to Review  
FDA Approved Drugs**

**Streamlined Pipeline for  
Repurposed Drugs**

**Templates for Clinical  
Trials Designs**

**Guides for Regulatory  
Compliance**



**Aging-Related  
Outcomes “Toolkit”**

**Central Geroscience  
Biobank**

**Core Facilities for  
Biochemical Assays**

**Specialized Centers  
for PoC Clinical Trials**

A photograph of the Golden Gate Bridge in San Francisco, California, taken during sunset. The bridge's iconic orange-red towers and suspension cables are silhouetted against a warm, orange and yellow sky. The bridge spans across the water, with the city skyline visible in the distance. The foreground shows a rocky, grassy hillside.

**Thank you!**  
**newman@ucsf.edu**  
**@AgingSciDoc**

