Designing the Aging Outcomes Trial Targeting Aging with MEtformin (TAME)

Jamie N. Justice, Ph.D.
Assistant Professor, Internal Medicine - Gerontology & Geriatrics
Wake Forest School of Medicine, Winston-Salem, NC
2019 State of the Science Symposium, Bethesda, MD, Oct 25, 2019

Wake Forest™ School of Medicine

Conflicts to Disclose

- None

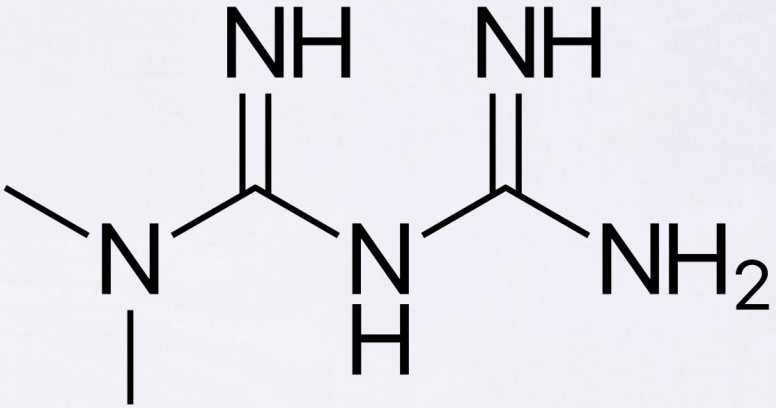
TAME: Aging Outcomes Trial

- Targeting Aging with MEtformin (TAME)
  - 6-yr Double Blind Randomized Placebo Controlled Trial
  - N=3000 nondiabetic adults aged 65-80 yrs
  - 14 US clinical study sites
  - Metformin dose: 1500 mg slow release 1x per day

- **First Aging Outcomes Trial**
  - Create a regulatory path for clinical trials to target age-related multimorbidity

- Funding: American Federation for Aging Research
  - Pending: NIA's Division of Aging Biology - support for TAME's Biorepository & Biomarkers Core

Geroscience

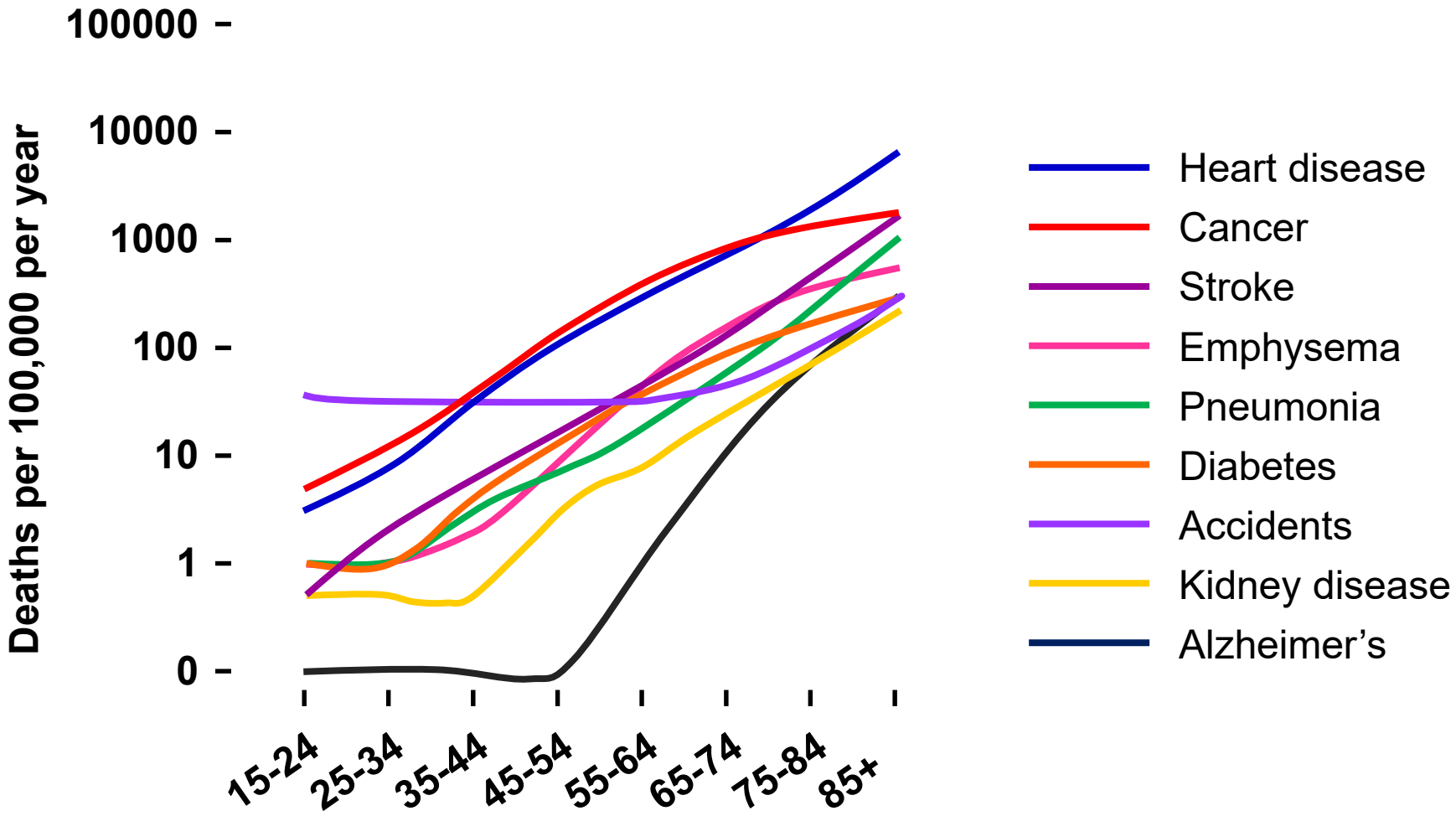


Metformin

Caloric Restriction

Geroscience Premise:

Age is the strongest risk factor for chronic diseases.



Millbank Quarterly. 80(1). 2002. (from 1997 U.S. Vital Statistics)[5]

Geroscience Premise

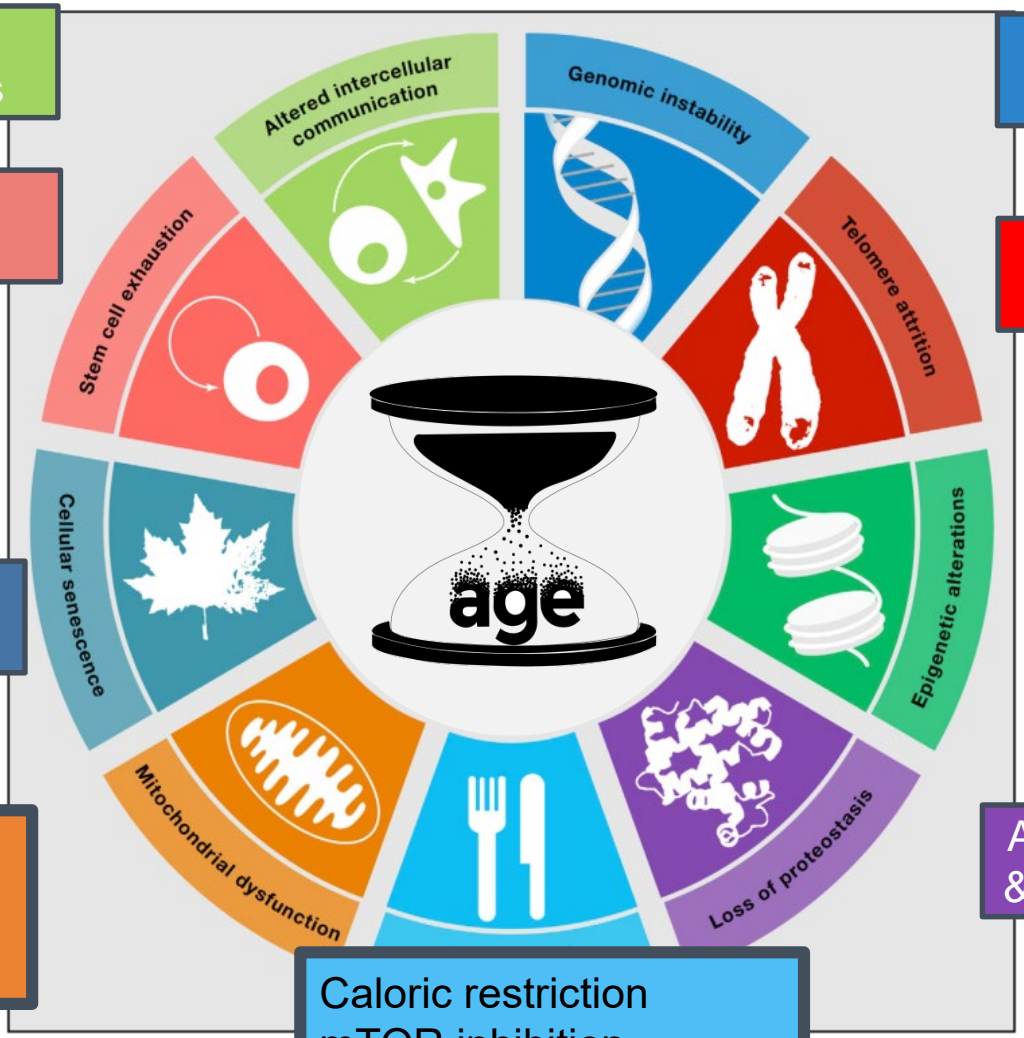
Intervene on biological aging process to extend healthy lifespan

Anti-inflammatory & Blood-based factors

Stem cell based therapies

Senotherapeutics: clear senescent cells

Mitohormetics
Mitophagy activators
Mito-targeted antiox



Caloric restriction
mTOR inhibition
AMPK, Sirtuin Activation

Autophagy activators & Proteolytic systems

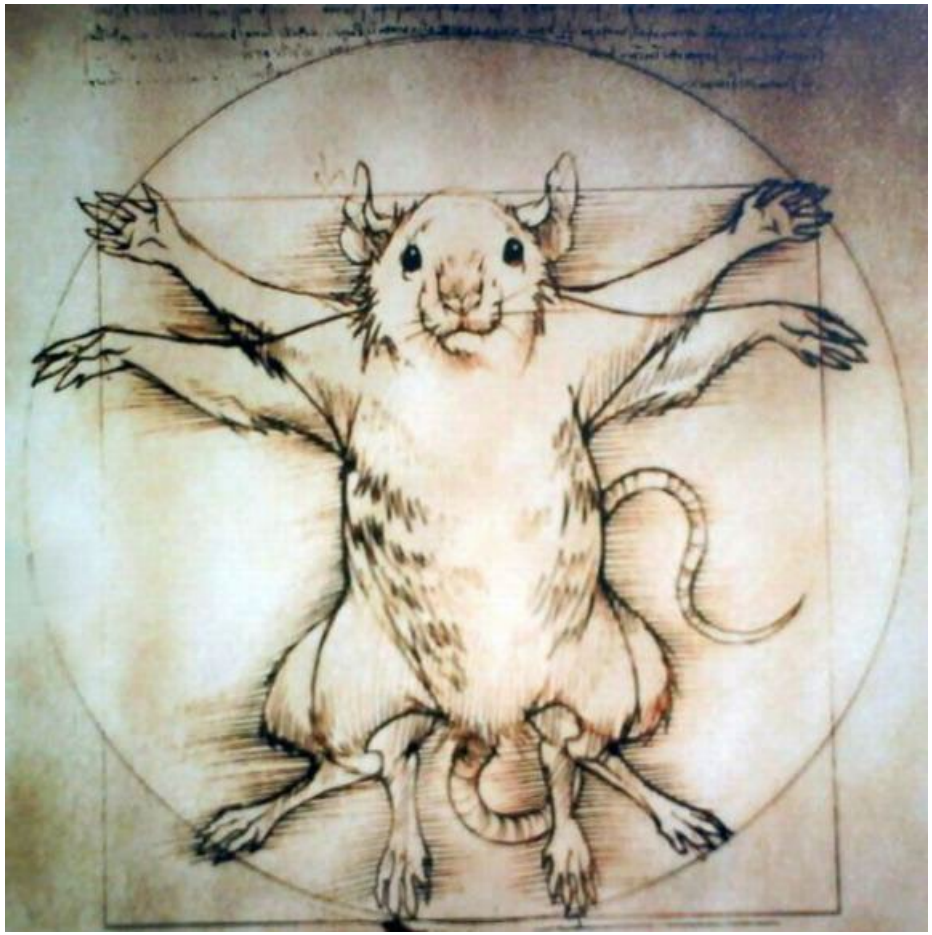
Telomerase Reactivation

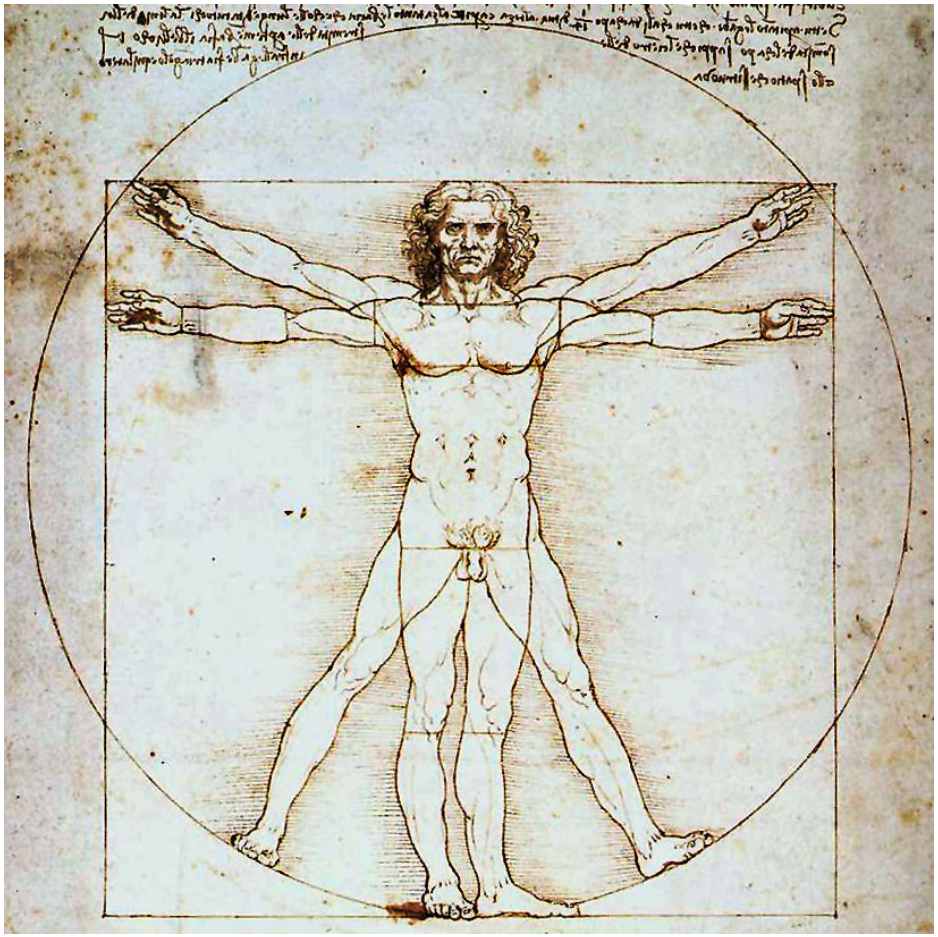
Elimination of damaged cells

Geroscience Premise

- Age is the strongest risk factor for our most burdensome diseases.
- Aging has a distinct biology that increasingly is being understood.
- Diet interventions and small molecules targeting that biology extends healthy lifespan in animal models.

We are ready to test the gersocience hypothesis in humans





Key Trial Design Elements

- What experimental population?
- Which interventional tool to use?
- What outcome(s) to evaluate?

Populations for Geroscience Trials: What experimental population?

- There is an aspect of health which is more than the lack of pathology in individual organs.
- Functional measures tap into how a patient is doing as an **integrated system**.

Slow Gait Speed (0.4-1 m/s)

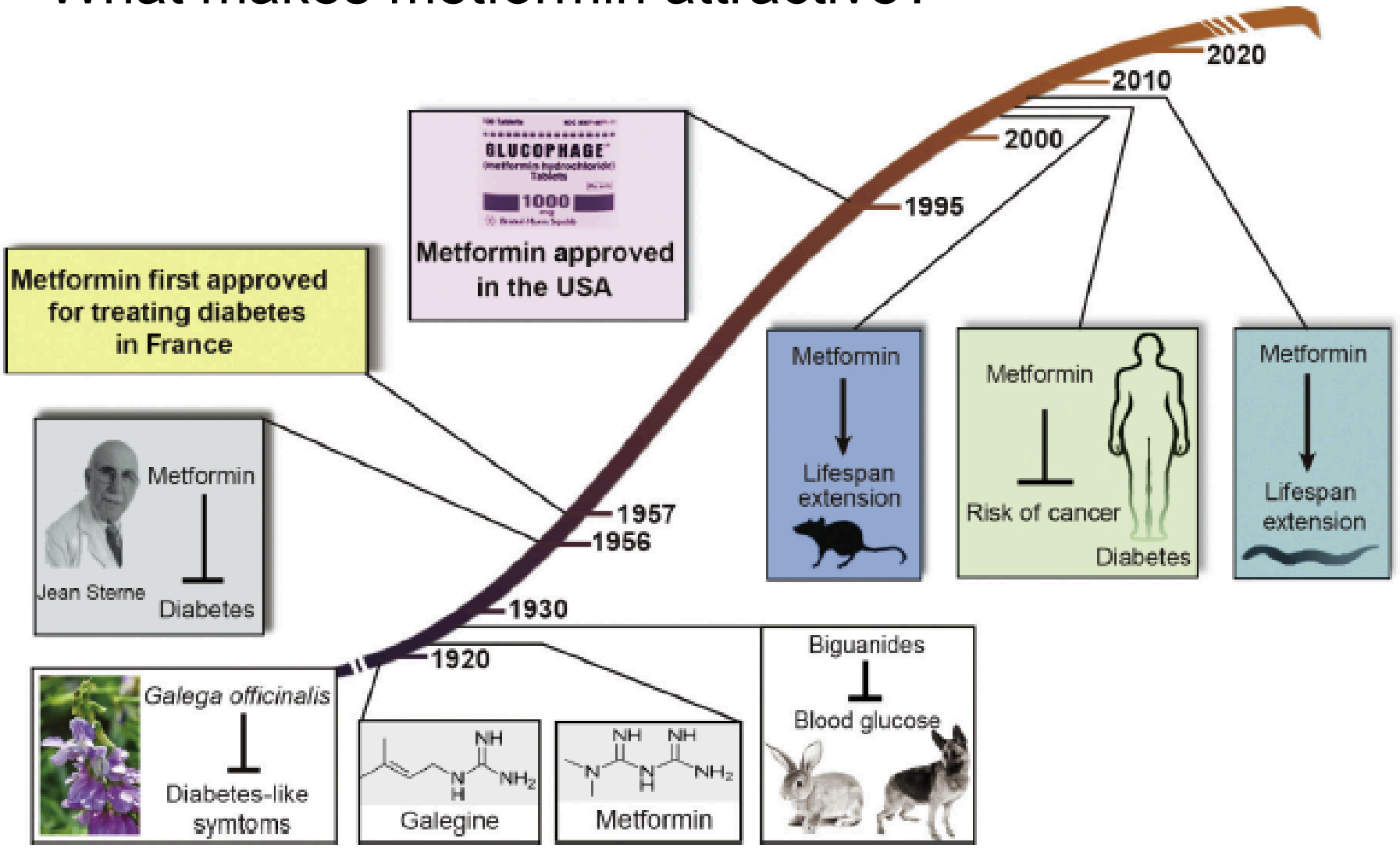
- ☑ Integrated Measure of Biological Age and Health Expectancy
- ☑ Indicator of Reserve & Stress Resistance
- ☑ Prediction Therapeutic Response

Key Trial Design Elements

- Who is an appropriate population?
- What interventional tool to use?
- What outcome(s) to evaluate?

Geroscience-Guided Interventions

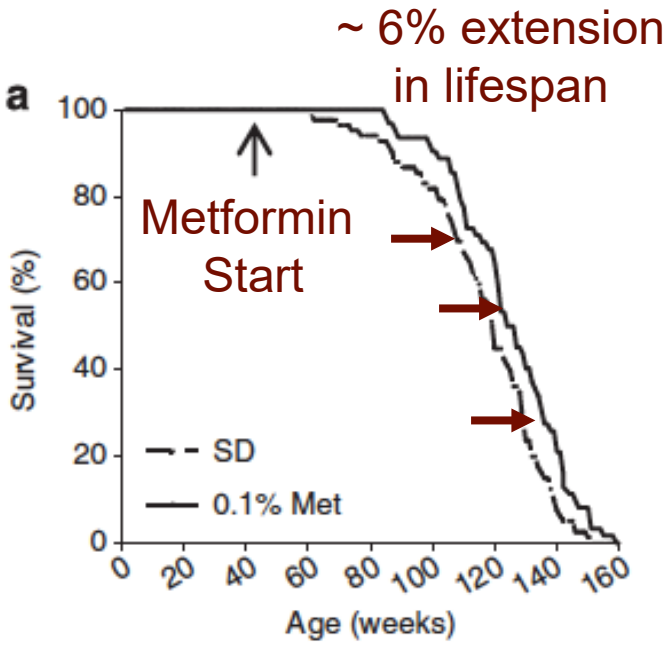
What makes metformin attractive?



Soukas, Hao, Wu. Trends Endo & Metab (2019), *in press*

What makes metformin attractive?

Metformin (at non-toxic doses) started at midlife increases lifespan and healthspan in mice



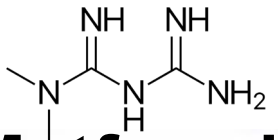
~25% Healthspan Benefit:

- Preserved body weight & body composition
- Shift in energy homeostasis and increased use of lipid
- Reduction in cataract development
- Improved general fitness and physical performance
- Lower HbA1c, insulin, HOMA-IR, LDL, total cholesterol
- Shift in gene expression
- Activation of AMPK
- Reduction of oxidative stress and enhance antioxidant defense
- Inhibition of chronic inflammation

Martin-Montalvo et al. Nat Comm (2013) 4: 2192.

Geroscience-Guided Interventions

What makes metformin attractive?



Metformin

Invertebrate Models

- Increases mean life span
- Induces youthful physiology
- Shows caloric restriction characteristics
- Presents better long-term survival after anoxia exposure
- Induces mitohormosis

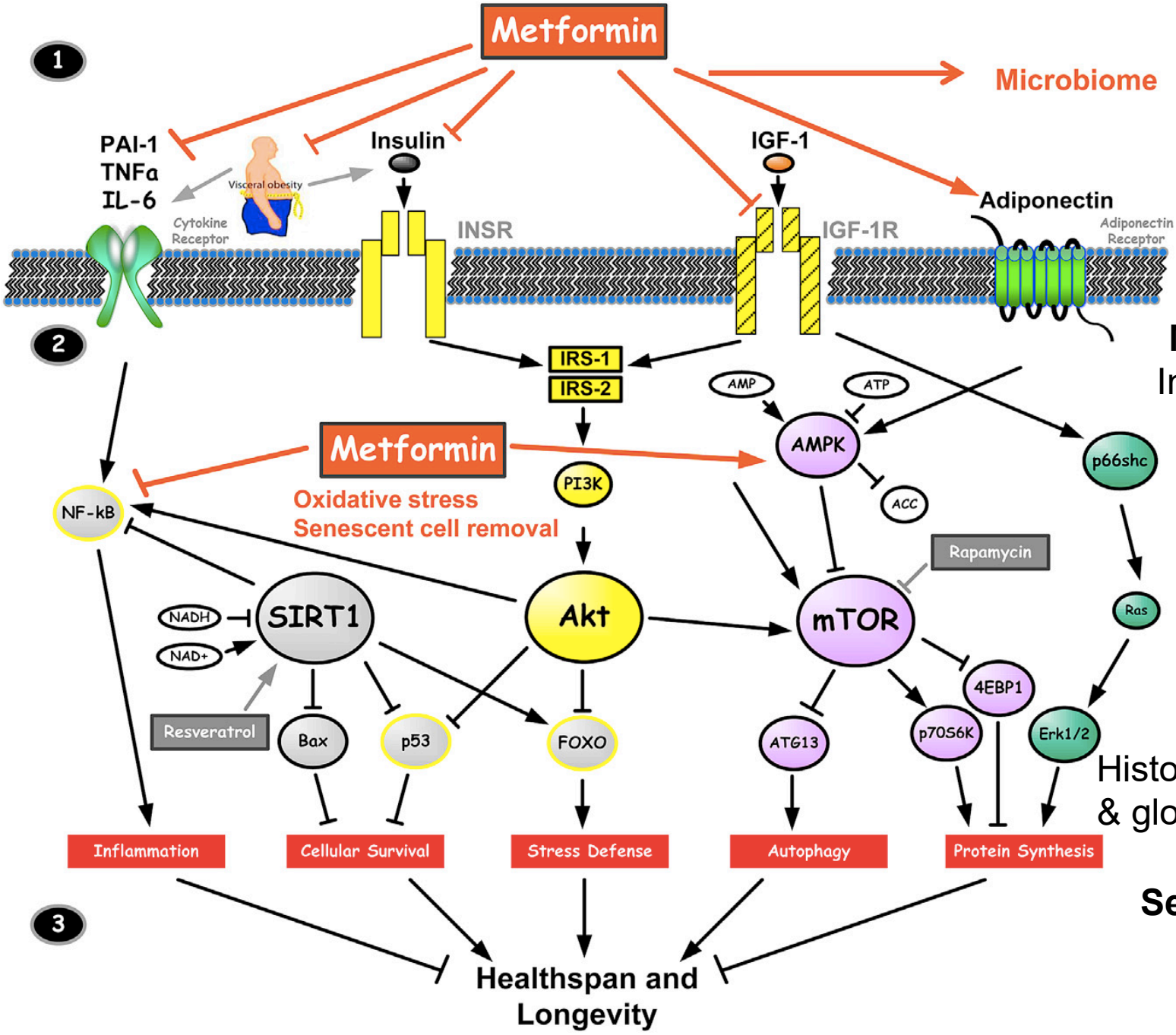
- Does not increase longevity
- Is toxic in a dose-dependent manner
- Causes intestinal perturbations
- Inhibits age- and oxidative-stress-induced DNA damage

Vertebrate Models

- Increases mean and maximum life span
- Has antitumorigenic properties
- Acts as caloric restriction mimetic

- Shows negative results in neurodegenerative disorder models
- Effects are gender dependent in some strains, different mechanisms of aging in female/males
- Effects depends on the age starting the treatment
- There is only one study published in rats

Novelle, et al CSH Perspect Med (2016); 6:a025932



Mitochondrial:
Inhibit complex I

↓ ROS & damage

Muscle Ox Capacity

DNA Damage

Epigenetic:
Histone modification & global methylation

Senotherapeutic

Barzilai, Cell Metab (2016) 23(6): 1060-1065.

Geroscience-Guided Interventions

What makes metformin attractive?

- Metformin modulates critical pathways in the biology of aging.
- Metformin has been used safely for over 60 years.
- Metformin is available as a generic drug and is inexpensive.
- Metformin reduces the onset of disparate diseases (epidemiologic evidence).

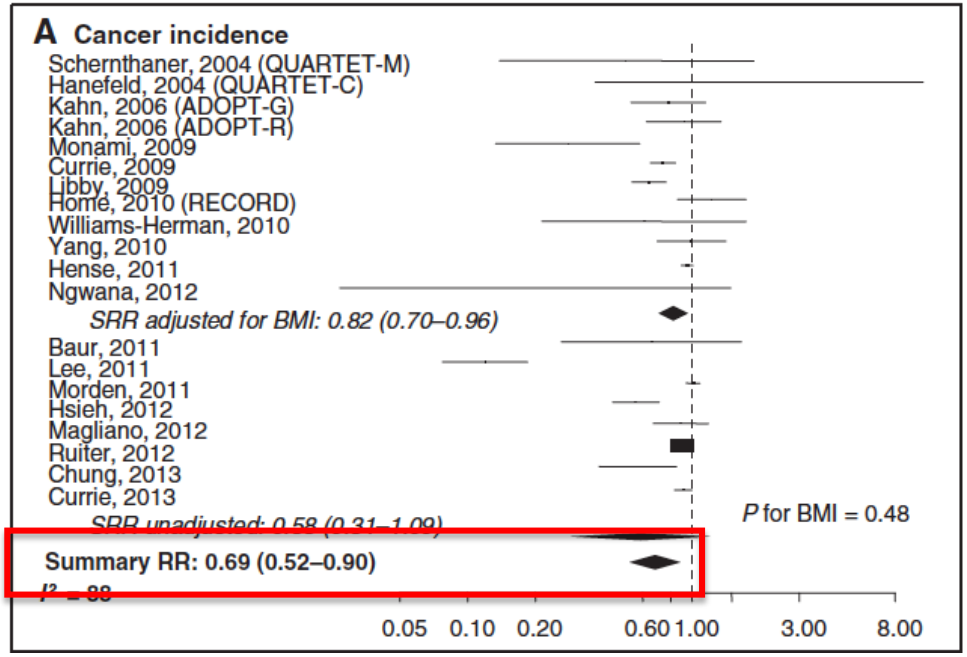
Metformin & CVD Outcomes (observational)

What makes metformin attractive?

Observational studies	Population	Comparator	Outcome	Effect size
Roumie (2012)	VA /Medicare database	Sulphonylurea	MACE	**21%** (HR 1.21)
Johnson (2005)	Canadian Rx drug database	Sulphonylurea	CVD hospital or death	**19%** (HR 0.81)
Schramm(2011)	Danish population	Sulphonylurea	MACE	**19-32%** (HR 1.19-1.32)
Roussel (2010)	T2D w/CVD or risk factors	Non-use	mortality	**24%** RRR (HR 0.76)
Masoudi (2005)	Medicare: T2D hospital CHF	T2D meds (not sensitizers)	Mortality Readmission for CHF	**13%** RR (HR .87) **8%** (HR 0.92)
Aguilar (2011)	VA patients with CHF	Non-use	Mortality	**24%** RR (HR 0.76)

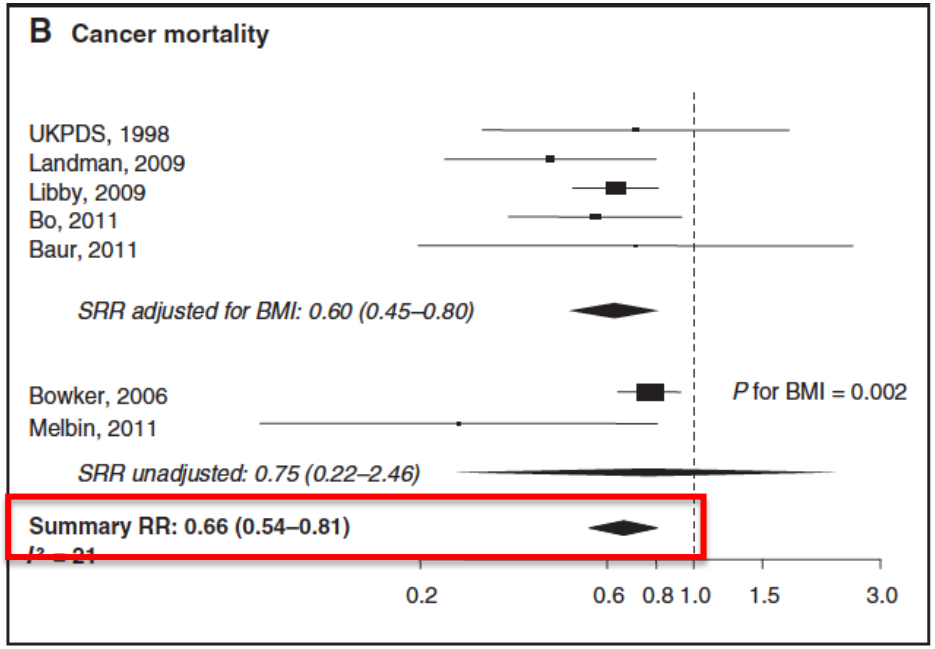
Metformin & Cancer Outcomes (observational)

What makes metformin attractive?



31% ↓Cancer Incidence

33% ↓ Cancer Mortality

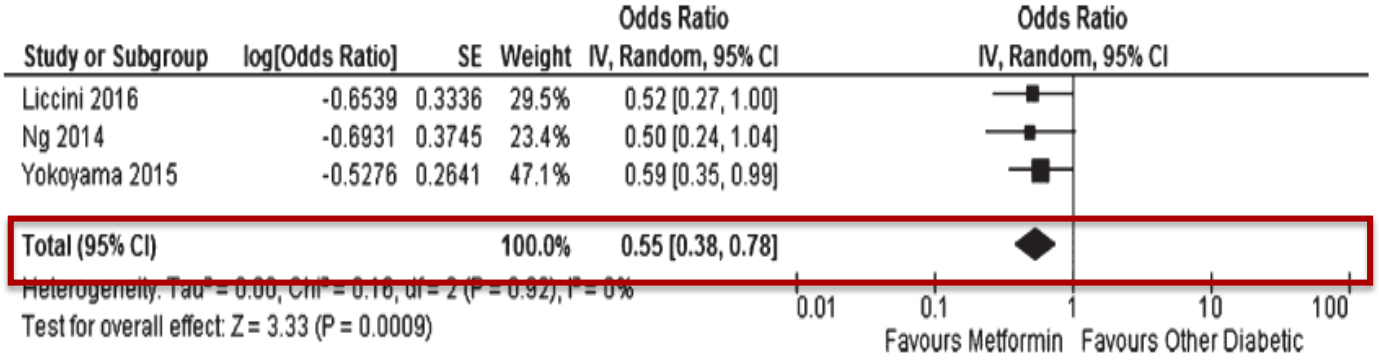


Gandini, et al. Cancer Prev Res (2014);7:867-85

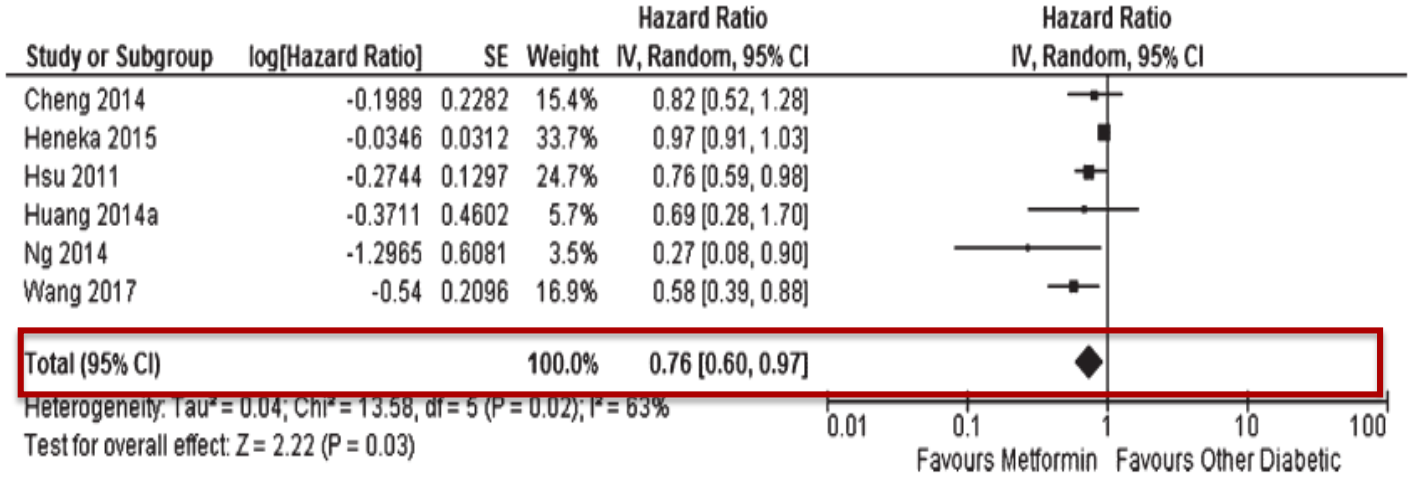
Metformin & Cognitive Impairment / Dementia

What makes metformin attractive?

Cognitive Impairment **45%↓**



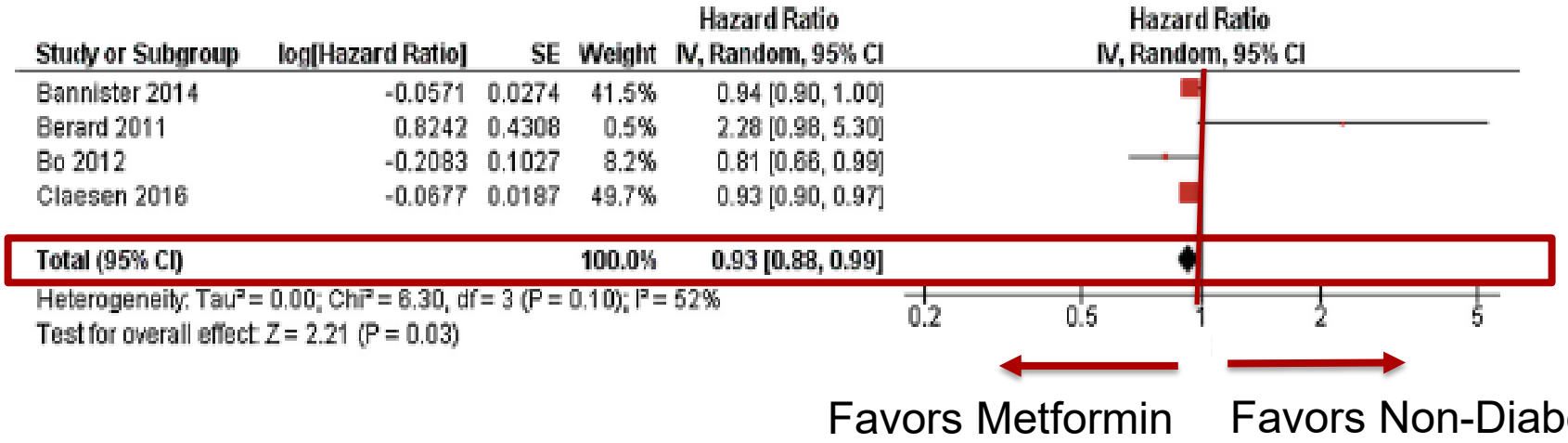
Dementia or AD **24%↓**



Campbell et al, J Alzh Dis (2018);65: 1225-38,

Metformin & All-Cause Mortality

What makes metformin attractive?



7%↓ All Cause Mortality for type 2 diabetic patients taking metformin vs. non-diabetics

Campbell et al. Aging Res Rev (2017) 30:31-44.

Overview of Epidemiologic Evidence

What makes metformin attractive?

Disease	Strength of association	
Prevention of type 2 diabetes	++++	**Obsv. Meta-Analysis**
Prevention of CVD	+++	20% MACE or mortality
Prevention of cancer	++	31% incidence, 33% mortality
Prevention of dementia	++	45% MCI, 24% AD
Reduction in mortality	+++	7% vs. nondiabetics
		Up to 28% all non-metformin controls

Negative studies? Contrary associations?
Of Course! **State of Equipoise**

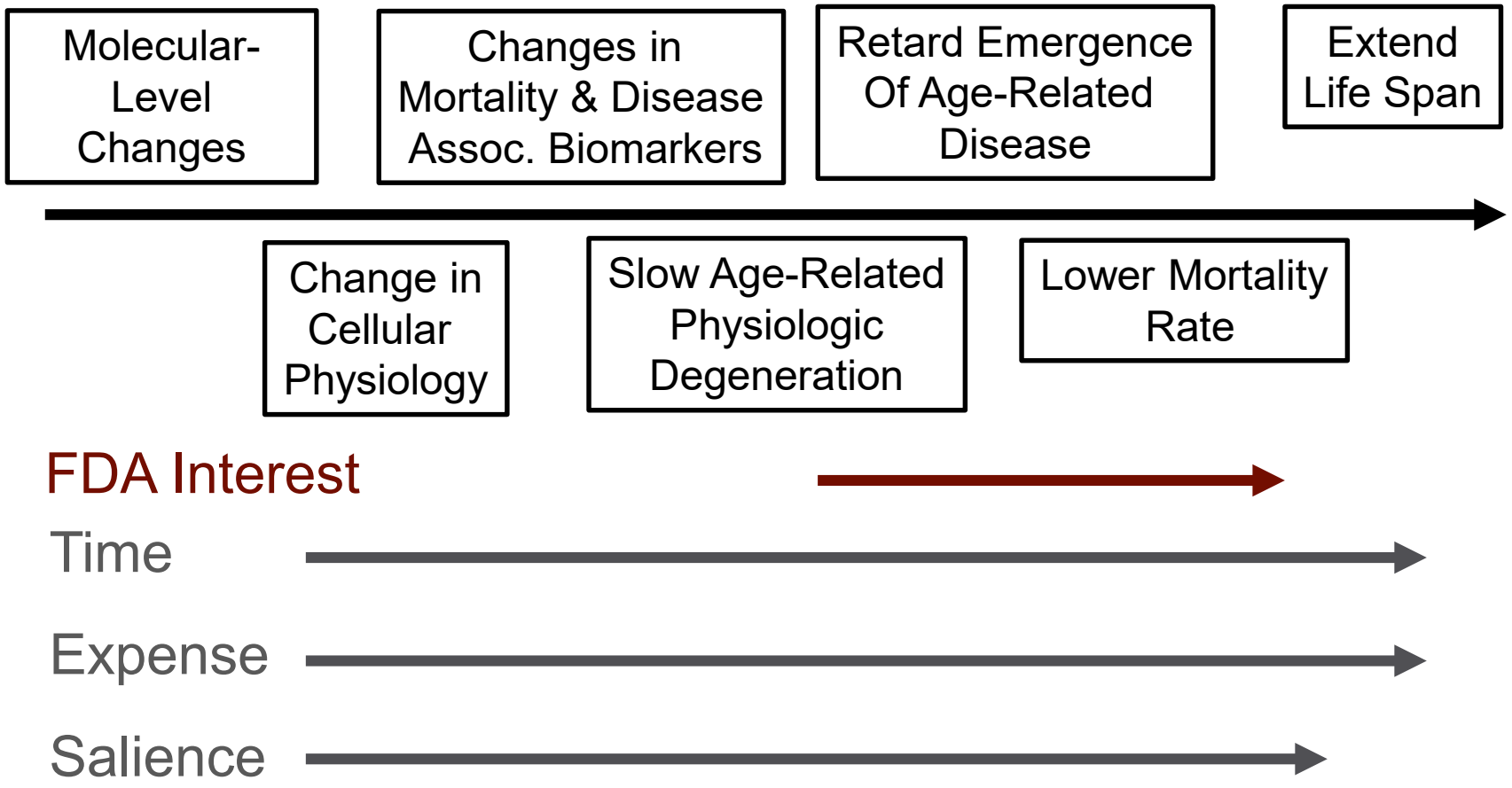
Barzilai, et al. Cell Metab (2016)

Key Trial Design Elements

- Who is an appropriate population?
- What interventional tool to use?
- What outcome(s) to evaluate?

Evaluation Continuum

What outcomes & biomarkers to evaluate?



Outcome to Test Geroscience Hypothesis

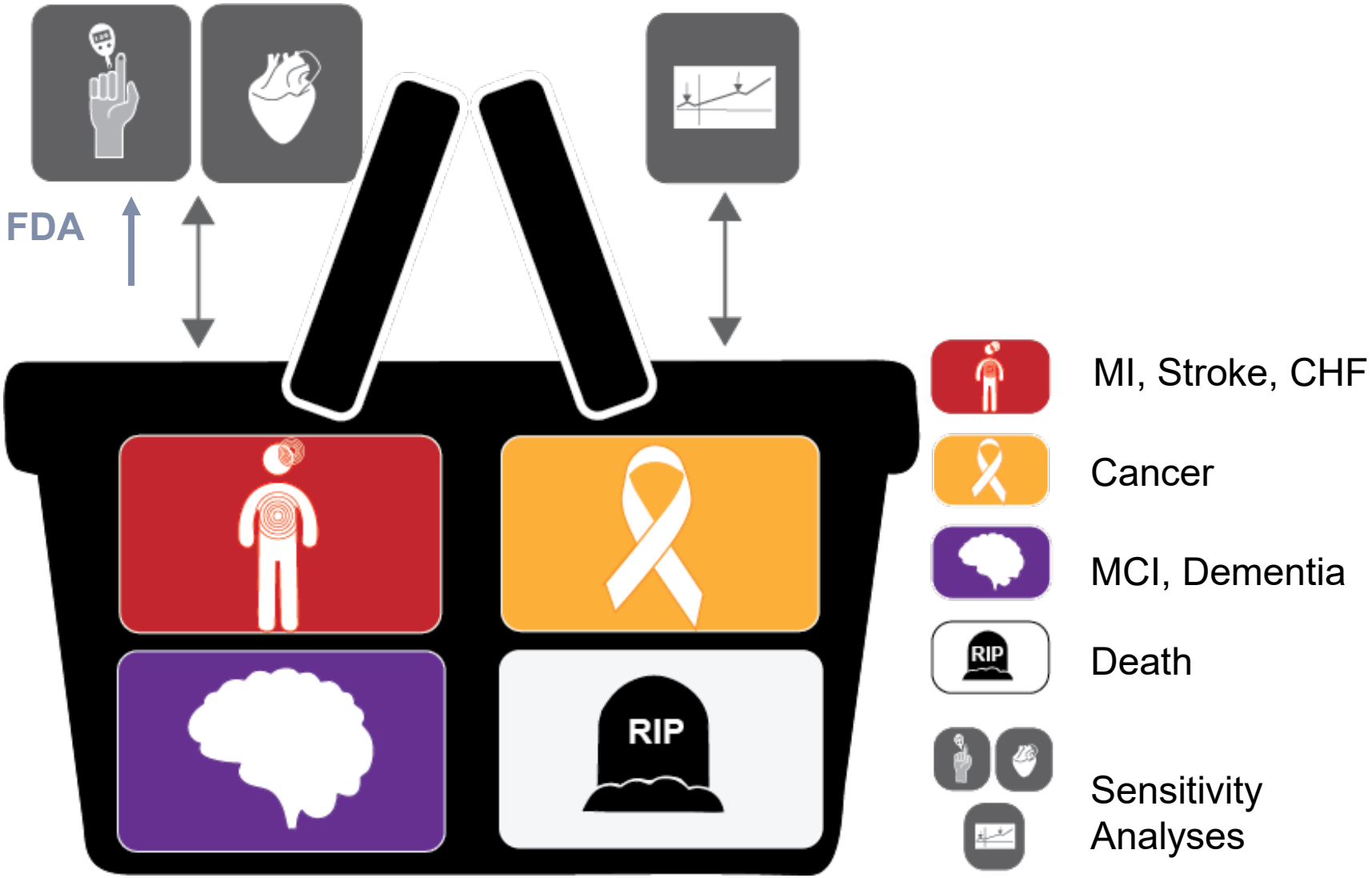
What outcomes & biomarkers to evaluate?

- If a drug's effect is on aging it should:
  - Reduce the incidence of multiple diseases
  - Diseases should share few risk factors other than age

- The outcome of interest is the time to occurrence of one of a collection of possible disease endpoints.

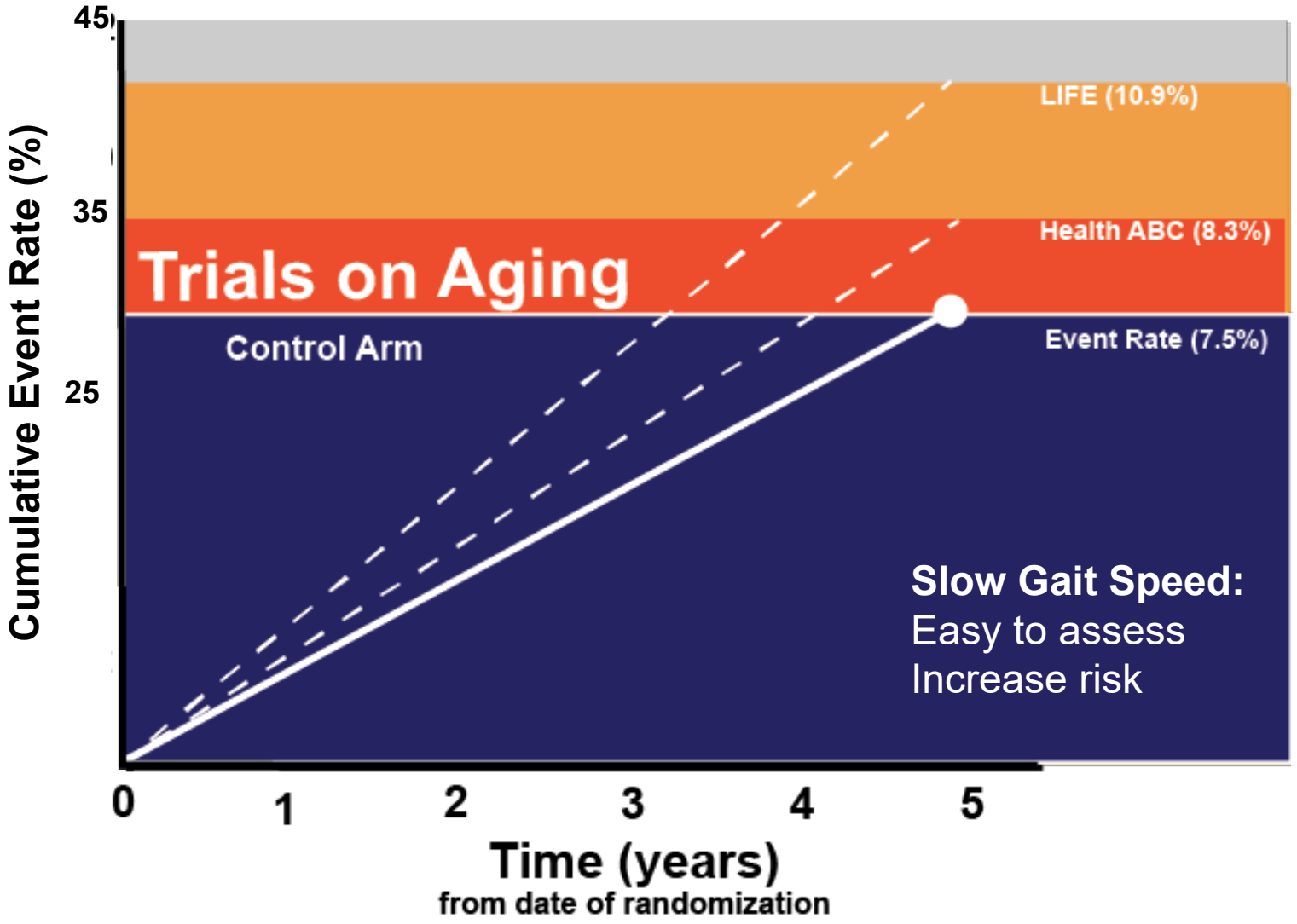
Outcome to Test Geroscience Hypothesis

What outcomes & biomarkers to evaluate?



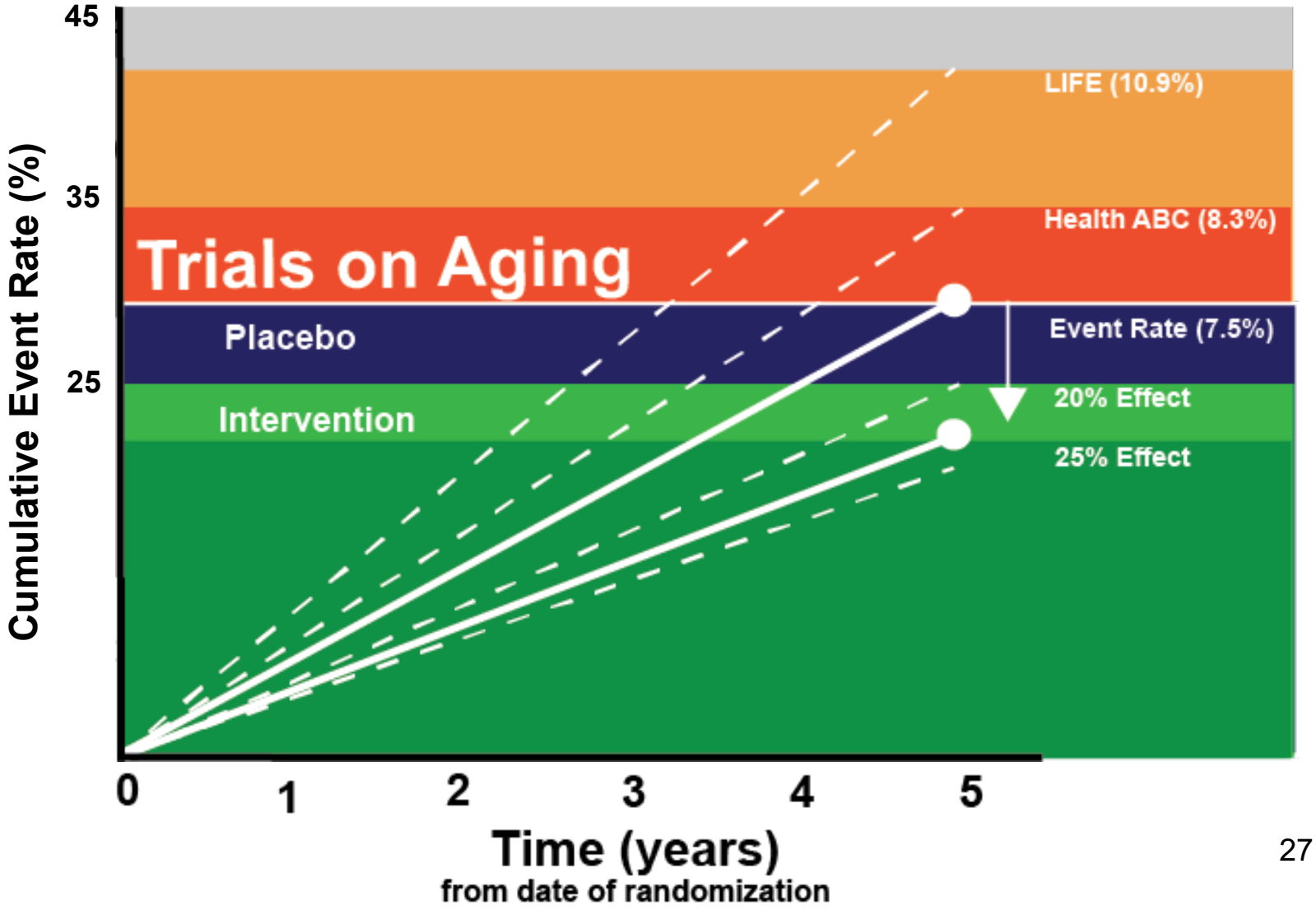
Outcome to Test Geroscience Hypothesis

Age-related multimorbidity disease outcome



Outcome to Test Geroscience Hypothesis

Metformin effect on age-related multimorbidity



TAME Aging Outcomes Trial

Age 65-80 years AND
Slow gait speed OR Age-related disease

Inclusion Criteria

Metformin (1500 mg 1×/day)
vs. Placebo (0 mg 1×/day)

n = 3000, 6-year, 14 Clinical Sites; double-blind randomized placebo controlled trial

(**Clinical**) Time to incidence of any age-related disease:
MI, stroke, CHF, cancer*, MCI/dementia, or death.

Primary Outcome

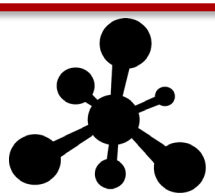
(**Functional**) Decline in mobility or cognitive function.

Secondary Outcome

AFAR Funded Aging Outcomes Trial

Pending: NIA, Div Aging Biology: U19 Biorepository & Biomarkers

(**Biological**) Change in biomarkers of aging.



Resource & Biomarkers Outcomes

* Excluding non-melanoma skin cancer and prostate cancer

Collaboratively designed: Investigators, FDA regulatory officials, NIH & key stakeholders

get people in the same room; cross-discipline communication is key

NIH
NIA

afar
american federation for aging research

TAME Trial Timeline

2013				R24 Geroscience Network
2014		TAME Executive Committee Formed	Network Retreat, Santa Barbara, CA	Network Retreat, Oroposa, Spain
2015	FDA Meetings, Silver Springs, MD	Network Retreat, Santa Barbara, CA	Application to NIA's Clin Trial Advsry Panel	Network Retreat, New Castle, UK
2016	Revised App. to NIA's Clin Trial Advisory Panel (CTAP)		Assemble 14 Clinical Sites, Drug Distribution, Central Lab, Steering Committee	
2017	U19 Application to NIA	Refine Protocol, Regulatory Approvals	Develop & Refine Trial Biomarkers of Aging & Biorepository Strategy	
2018	Metformin pilot Studies published	Revised U19 Application. to NIA	Pre-IND submitted to FDA	
2019	Revise budget for AFAR	Start-up & FDA Compliant Database	U19 NIA for Biomarkers Strategy	Recruitment starts, 2020

Considerations

Gaps & Future Investment

Investments:

- Interdisciplinary research and clinical networks & shared resources
- Translational pipeline to advance promising interventions to trials
- Reverse translation: use clinical trials in aging to drive discovery, refine interventions & disease models
- Funding opportunities for clinical trials with age-related multimorbidity

Gaps:

- Validated biomarkers of biological aging for clinic / clinical trials?
- Combined therapies: metformin + caloric restriction, exercise, etc.?
- Metformin as a caloric restriction mimetic in humans?

Thank you!

afar

american federation for aging research

NIH

NIA

Wake Forest School of Medicine

TAME Executive Committee

Nir Barzilai
Mark Espeland
Stephen Kritchevsky
Vanita Aroda
George Kuchel
Jamie Justice

AFAR; Glenn Foundation; NIH: K01 AG059837-01 (JNJ), P30 AG021332 (SKB, JNJ); R01 AG048023, R01AG052608, R35 GM124922 (GAK); P30 AG038072 (NB). Supported in part by NIA Intramural Research Program.