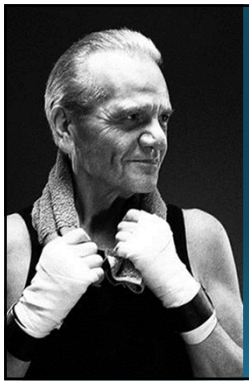

Longevity Medicine: a clinical primer

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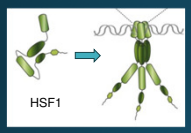
1

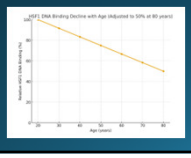
Disclosures

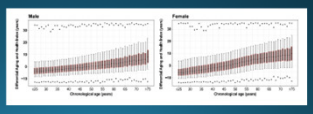
Dakota GERIATRICS
A HRSA Geriatrics Workforce Enhancement Program

2

Scientific background







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Longevity Medicine

- Slow the clock
- Extend quality life

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Goals

- Describe fundamentals of biological aging and its measurement
- Report biological targets for anti – aging interventions
- Define Longevity Medicine and current approaches

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Why engage Longevity Medicine?

- New evidence about slowing and reversing aging processes
- Slow aging to delay or prevent chronic conditions
- Compress the morbidity curve and increase quality years
- Biological aging as a clinic metric for interventions
- Improve quality, lower health care costs

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Is Aging Necessary ?

View A

Aging unavoidable, biological breakdown

Disease oriented treatment

View B

Prevent Aging

Slow or reverse aging processes

Conundrum: Does evolution select long life or lifespan ?

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Table 1. Normal gait speeds for healthy community-dwelling men and women.[11]

Age (years)	Gender	Average Gait Speed (m/s)
20-29	Men	1.36
	Women	1.34
30-39	Men	1.43
	Women	1.34
40-49	Men	1.43
	Women	1.39
50-59	Men	1.43
	Women	1.31
60-69	Men	1.34
	Women	1.24
70-79	Men	1.26
	Women	1.13
80-89	Men	0.97
	Women	0.94

Workshop: biological aging metrics

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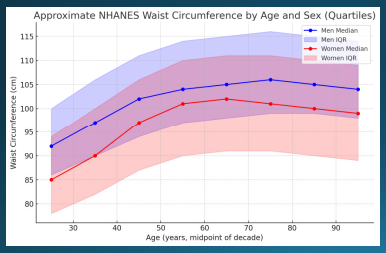
Waist circumference and aging



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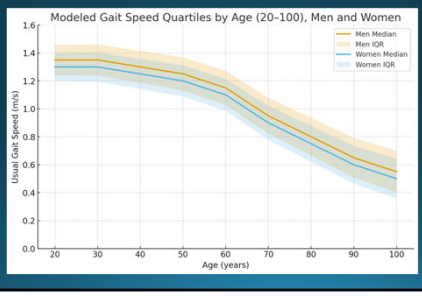
Gait Speed and aging



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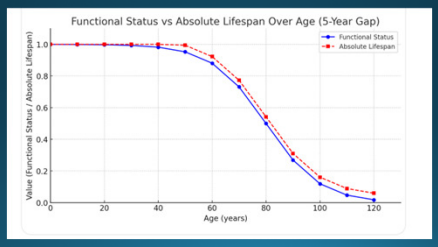
Difference between functional (years free from disability) and absolute (total years lived) lifespans



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THEORIES OF AGING

1923 WASTE PRODUCT THEORY
Carrell & Ebeling
1924 WEAR & TEAR THEORY
Pearl
1928 RATE OF LIVING THEORY
Pearl
1947 ENDOCRINE THEORY
Korenchevsky & Jones
1955 FREE RADICAL THEORY
Harman
1957 COLLAGEN THEORY
Vezar
1959 SOMATIC MUTATION
Sziliard
1963 ERROR CATASTROPHE
Orgel
1968 CROSS LINK THEORY
Bjorksten
1968 PROGRAMMED SENESCENCE
Hayflick
1969 IMMUNE THEORY
Walford
2000 EPIGENETIC
Horvath

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Biology of Aging

- Molecular → Cellular → Organ changes

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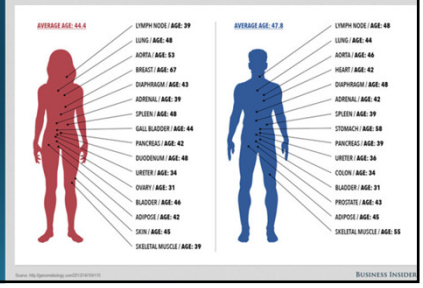
Organs do not age at the same rate!



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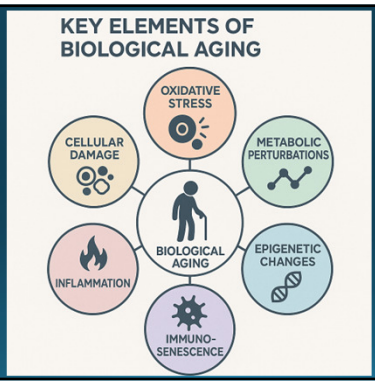

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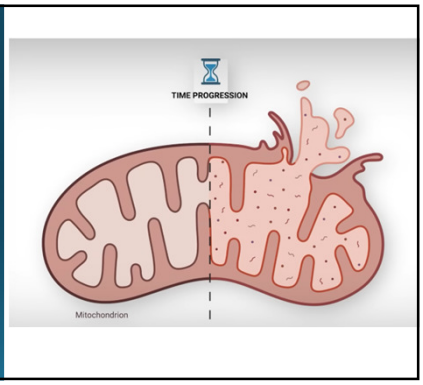
Metabolic changes with age

- Basal metabolic rate decreases 0.7% annually
- 1 carbon chain deficit
- NAD and bioenergetics
  - Fewer and less efficient mitochondria
- Insulin resistance



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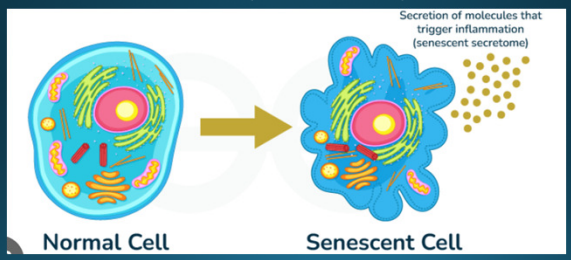
Cellular damage with age



Autophagy, proteostasis and stress responses decline

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Immunosenescence and inflammaging

- Innate immunity
  - less phagocytosis
- Adaptive immunity
  - fewer naïve and more memory T cells driven by chronic viral suppression
  - reduced antibody repertoire
- Cytokine storms

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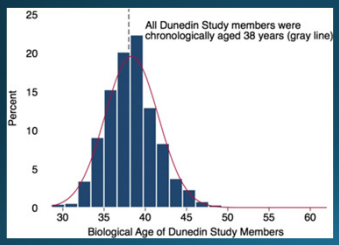
Biological Age



Measurement

DNA methylation patterns

Physiologic / blood markers

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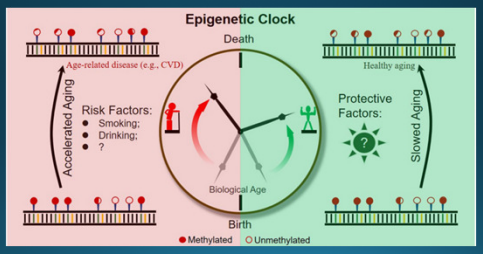
Measuring biological age



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Composite Biological Clocks

- Anthropometrics: BMI, waist circumference
- Vital signs: blood pressure
- Renal: BUN, creatinine, eGFR
- Liver: AP, SGOT, SGPT, GTTP
- Metabolic: FBS, HA1C, albumin
- Lipids: Cholesterol, TG, HDL, Lipoproteins
- Immune: WBC count, CRP, % lymphocytes
- Hematologic: RDW, MCV
- Pulmonary: FEV1

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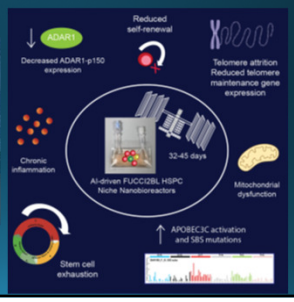
Aging accelerants: space



Stem cell and progenitor cell aging
Cell Stem Cell (2025) /doi.org/10.1016/j.stem.2025.07.013

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Aging accelerants: sedentariness

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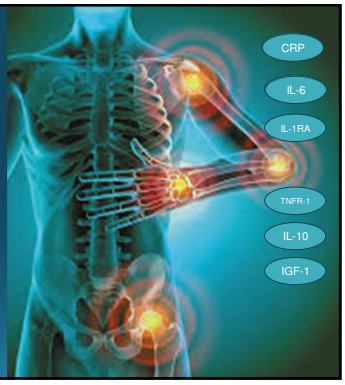
Aging accelerants

Inflammaging

- IL-6 elevati0n ~ 1.0 year lifespan reduction[1]
- CRP elevation RR 1.2 for death with every 10 mg / dL CRP rise[2]
- Low wealth synergizes with elevated CRP effects[3]
- Inflammatory bowel disease reduces lifespan from 5 – 8 years[4]



1. doi.10.1210/jc.2010-0473
2. doi.org/10.1161/01.ATV.20.4.10
3. doi. 10.1016/j.annepidem.2021.12.007
4. doi. 10.1503/cmaj.190976

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Aging accelerants: sleep quality

- Low sleep risk factors associated with increased lifespan, extra 4.7 years for men and 2.4 years for women (National Health Interview Survey) [1]
- UK Biobank – actigraphy sleep study showed 29% increase in all cause mortality with 5 vs 7 hours nightly sleep
- European study – U shaped curve of healthspan with optimal between 7.0 – 8.5 hours

1. doi.org/10.1093/qjmed/hcad237
2. doi.org/10.1093/sleep/zsad312
3. Doi. org/10.1093/gerona/glyo16

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Aging accelerants: stress

- High self - reported stress increased HR for death to 1.17 [1]
- Dose response association between psychological stress and mortality (HR = 2.26 for highest stress levels)[2]
- High nocturnal cortisol levels increase CV risk (HR = 1.49) [3]

1. doi:10.1001/jamanetworkopen.2021.38920
2. doi.org/10.1136/bmj.e4933
3. doi:10.1016/j.psyneuen.2022.105753

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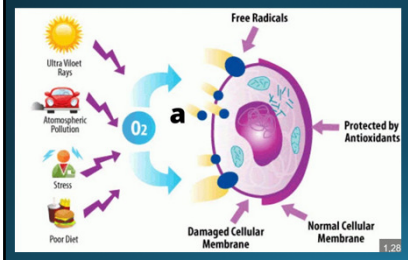
Aging accelerants: oxidant injury



- Highest quartile of urinary isoprostanes had 80% higher risk CV mortality [1]
- High serum hydroperoxides associated with HR = 2.10 for all CV mortality[2]
- SOD knockout mice have 30% shorter lifespans[3]

1. dio.10.1016/j.jacl.2008.06.004
2. dio.org/10.2337/dc19-0292
3. dio.org/10.1016/j.freeradbiomed.2009.03.025

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Agents studied for healthy lifespans

Class	Examples	Mechanism
Bioenergetics: NAD + booster	Nicotinamide Ribose	Increase NAD, activate sirtuins, mitochondria, DNA repair
Autophagy / mTOR inhibition	Metformin, rapamycin, spermidine	AMPK/mTOR modulation, better autophagy & proteostasis
Inflammaging / Senolytics	Fisetin, Quercetin (±Dasatinib)	Clear senescent cells and suppress inflammation
Metabolic / AMPK activators	Berberine, ALA, EGCG	Energy sensing & insulin sensitivity
Senomorphics	Curcumin, Boswellia	Suppress inflammation, improve stress response Anti oxidants
Anti oxidants	N acetyl cysteine, sulforaphane	
Caloric restriction mimetics	Resveratrol	Sirtuin & AMPK activation

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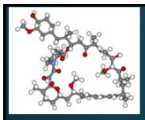

Rapalogs / mTOR inhibition

- 20% improved flu vaccine response in older adults[1]
- Reduced circulating T cells with programmed death receptor – 1 (PD-1)
- No difference preventing URI's [2]

1. Science Translational Medicine (2014) doi.10.1126/scitranslmed.3009892
2. Lancet Healthy Longevity 2:E250, 2021

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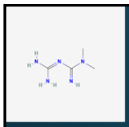

Metformin: mTOR inhibition

- Targeting Aging with Metformin (TAME) study
  - No published results
- UK Biobank (Lancet Healthy Longevity, Volume 4, Issue 7e337-e344July 2023)
  - Lower Phenotypic Age
  - No change in leukocyte telomeres

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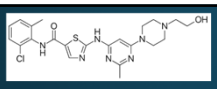

Senolytics

Dasatinib & Quercitin (Tyrosine kinase inhibitor)

- 2019: Idipathic Pulmonary Fibrosis: better physical function (6M walk) but no change in pulmonary function [1]
- 2019: Diabetics: reduced inflammatory markers and p21 senescent cells. [2]

UBX0101 (p53 stabilizer for apoptosis)

- knee osteoarthritis: one intra – articular dose, no effect.

Fenestin (BCL-2 inhibitor and attenuator of mTor & NFKB)

- 2024: reduce sepsis events in older adults, results pending

1 Lancet eBioMed 40:554, 2019
2 Lancet eBioMed 47:446, 2019
3 Trials 25:698, 2024

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Organelle therapy: mitochondria

- Natruceuticals: resveratrol, urolithin A, nicotimamide
- Caloric restriction: improve nutrient sensing pathways
- Exercise: both aerobic and anaerobic to increase biogenesis, respiration and protein$_{mt}$
- Mitochondrial transplants

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Organelle therapy

Organelle	What goes wrong	Target / Strategy
Nucleus	Nuclear lamina, nuclear pores, and rDNA transcription	Lonafarnib inhibits farnesyltranferase (extends Progeria lifespan)
Lysosomes	Defective acidification and cargo processing	Boost Transcription Factor EB (TFEB)
Proteosomes	Activity declines	Small molecule proteasome activators (TCH-165, IU1
Endoplasmic reticulum	ER proteostasis declines	Modulate integrated stress response
Peroxisomes	Reduced ROS management, biogenesis, and importation	PPAR agonists and plasmalogen (for cognitive aging)

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Bioenergetics

- NAD+ boosting: goal of nicotinamide ribose to increase ATP, mitochondrial biogenesis and repair
  - British: 3W study showed minimal impact on mt proteins, biogenesis and bioenergetics (1 gm daily NR in 70 -80 y.o. men). Lower inflammatory markers.
  - Finish study: 5M, showed increased mitochondrial biogenesis and secondary effect of improved gut microbiota (1 gm daily)

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Summary of anti – aging agents

- Strong preclinical evidence and molecular foundation
- Many agents have pleiotropic effects
- Longevity pundits use combination therapies
- Best dose / schedule unknown
  - "Hit and Run" / hormesis, e.g., senolytics
  - Continuous therapy, e.g., metformin
- Active metabolites / resistance ?

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Exercise for longevity

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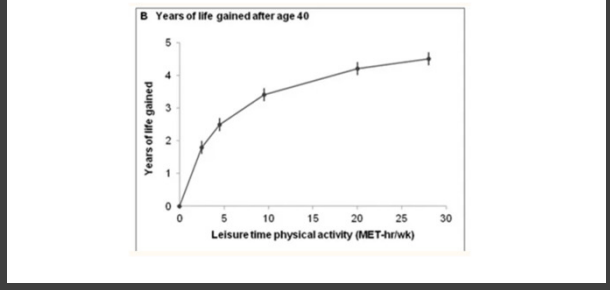

PLoS Medicine, 9(11): e1001335. https://doi.org/10.1371/journal.pmed.1001335

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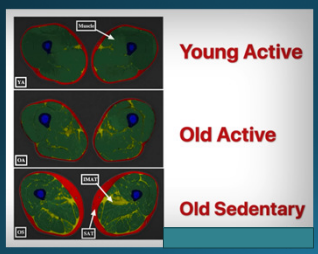
Good news: old = young



Green = muscle

Red = peripheral fat

Yellow = central fat

Mitochondrial protein levels comparable btw young and old active, while 50% less in sedentary old

DOI: 10.1113/JP273950

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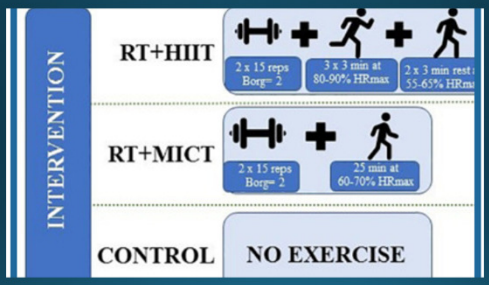

Doi 10.3389/fphys.2020.00572

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HIIT vs MICT metabolic syndrome

Test	Intervention	Pre	Post
Grip strength	Control HIIT	21.27 21.43	20.55 23.08
30 second sit – stand	Control HIIT	15.11 15.98	15.85 20.54
Gait speed	Control HIIT	1.80 1.81	1.77 1.97

Doi: 10.1519/JSC.0000000000001895

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HIIT impact

Study	Intervention	HIIT improvement
2017 Swedish study doi: 10.3389/fphys.2017.00562	M/F elite athletes	Heart Rate Recovery
2020 Brazilian study doi: 10.3389/fphys.2020.00572	M/F older adults (average = 67)	FBS and LDL No physiological difference vs. MICT
2022 Portuguese study DOI:10.1590/1517-8692202228042020_0122	M/F older adults w/ metabolic syndrome (average = 67)	VO2 peak
2024 Meta analysis (n = 44) doi: 10.1186/s40798-024-00767-9	Age range 60 - 81	Resting Heart Rate, Systolic BP, fitness and balance (TUG test)

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Exercise for longevity issues

- 1% muscle loss annually
- Law of diminishing returns with increasing age
- HIIT vs MICT
- Under powered studies
- Nutrition and protein intake not controlled
- Sleep and recovery not controlled
- Impact of medications not controlled (e.g., statins or anti – androgenics such as spironolactone)
- Exercise volume not clearly established

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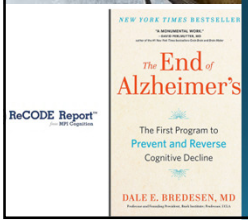

Nutrition for Longevity

- The case of the bone broth dietary cleanse

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Adventist Health study: additional life expectancy

Dietary pattern (HR)	Men	Women
Pesco-vegetarian (0.81)	+2.2 y	+2.1 y
Vegan (0.85)	+1.7 y	+1.6 y
All vegetarians combined (0.88)	+1.4 y	+1.2 y
Lacto-ovo (0.91)	+1.0 y	+0.9 y
Semi-vegetarian (0.92)	+0.9 y	+0.8 y

doi:10.1001/jamainternmed.2013.6473

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Reduction in overall and CV mortality

- **EPIC Greece**: high adherence to Mediterranean diet associated with HR = 0.75 all cause death (NEJM 348:2599, 2003)
- Nurses Health Study: improved diet quality garnered 17% less mortality over 12 years measured by Alternate Mediterranean Diet score (NEJM 377:143, 2017)
- NIH-AARP Diet and Health Study : replacement of animal with plant protein reduced overall and CV risk (JAMA Int Med 180:1173, 2020)

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Does Mediterranean diet change biological aging ?

- NU-AGE study: 1 YR Mediterranean diet slightly reduced biological age in Polish but not Italian women (Horvath Clock) *GeroSci 42:687, 2020*
- Central MRI study: 1.5 YR Mediterranean diet in obese Israeli men changed epigenetic age if diet led to weight loss. *Clin epigenetics 13:48, 2021.*

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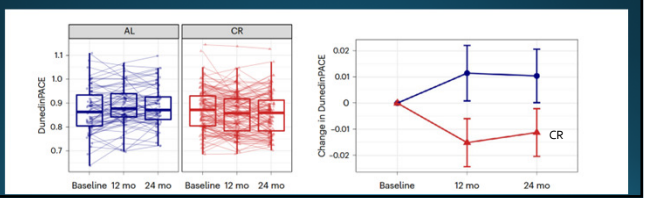
Caloric Restriction

- CALERIE: 2YR caloric restriction by 25%, only 12% acheived. DunnedinPACE changed (dynamic) but GrimAge and PhenoAge did not change (static) (DOI: 10.1016/S2213-8587(19)30151-2)



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Can intermittent fasting slow aging?

- Fasting Mimicking Diet (cycle of FMD x 5 days → usual diet 25 days →FMD x 5 days. 3 – 4 FMD cycles. FMD is ~ 717 kcal, plant – based 9% protein, 44% fat, and 47% carbohydrate (Nature Comm 15:1309, 2024) Reduced biological age by ~ 2.5 years (PhenoAge)
- 8:16 hour fasting vs 2:5 day fasting regimen: no biological aging data.

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How to prescribe longevity action plans

- **Preserve/build muscle**: 2–3 days/wk of resistance training .
- **Stay active daily** (walking/steps + some aerobic work) to support TEE as activity tends to drift down with age.
- **Prioritize protein** across meals and adequate sleep; both support muscle and insulin sensitivity. (e.g., 2 mg leucine for men with meal)
- **Track waist circumference and labs** (fasting glucose, A1c ± OGTT if at risk).

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AI Driven Longevity Center

New measurements of biological age
- Longevity transcription factors
- Resiliency tests
  - Physical
  - Cognitive

Person – centered longevity plan

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Resiliency Tests

Physiologic
- Heart Rate Recovery
- VO2max
- Grip strength exhaustion – recovery
- Sit – stand recovery
- Blood pressure variability / tilt test BP recovery
- Heart rate variability

Cognitive

Psychomotor vigilance test

Color Word Interference

Digit Symbol Substitution

Sustained Attention to Response Task

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Conclusion I

- Biological age and rate of aging are measurable
- Anti-aging interventions include diet, physical activity, stress reduction, sleep hygiene and possibly chemical adjuvants
- Prescriptions for healthy lifespans can be part of personalized medicine (2 – 4 extra healthy years)

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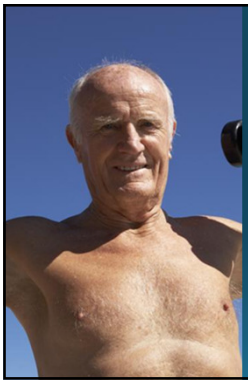

Conclusion II

- The Longevity Dividend seeks to reduce disability and disease in late life by slowing the rate of aging.
  - Extend both healthspan and absolute lifespan
- Anti – aging nutraceuticals, senolytics and organelle transplants hold promise for reversing age
- It's never too late to start a longevity plan

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