

Wellness Evolves Into Longevity: the Next and Most Major--14 shots on Goal

⋮
The Opportunity of a Lifetime—to be 40 again when the Calendar says 90

September 30, 2026

Michael Roizen, MD,FACP

*Chief Wellness Officer Emeritus,
Cleveland Clinic*

*Professor, Cleveland Clinic Lerner College of Medicine
at Case Western Reserve University*

Goals of Presentation: Back to 40 When the Calendar Says 90

1

You control your genes

and the proteins they produce.

2

You have to stay young

to get younger.

3

Get to “6 + 2”

The 6 Normals + 2: the foundation for sustained health.

4

14 shots on goal

6 already in humans, 2 available now: clear chronic disease, restore young cells, build a repair system, remove mis-signaling proteins.

5

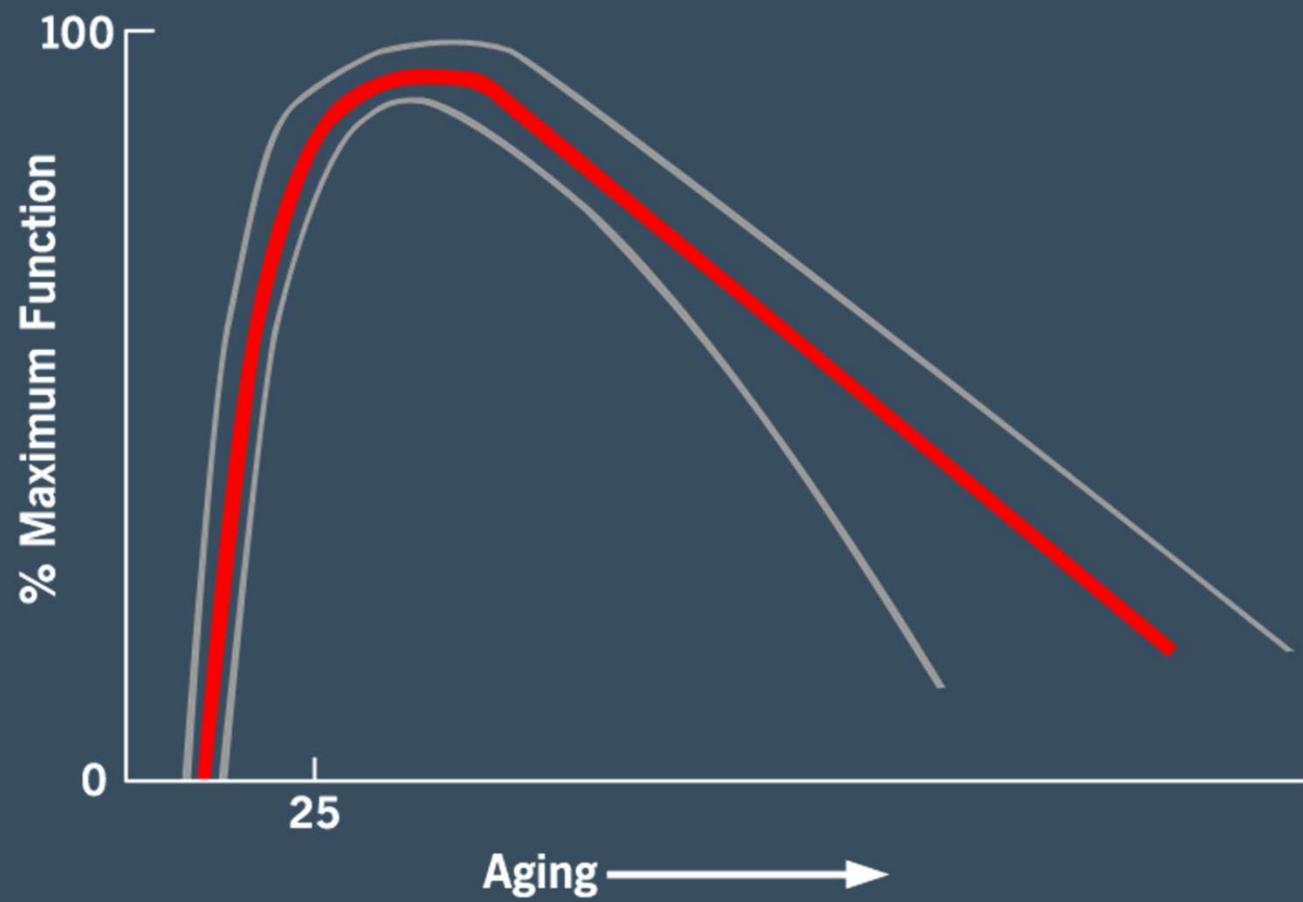
Hacks to stay young

including why almost everyone could talk with their doctor about baby aspirin, a statin, colchicine, a PDE5 inhibitor and a GLP-1.

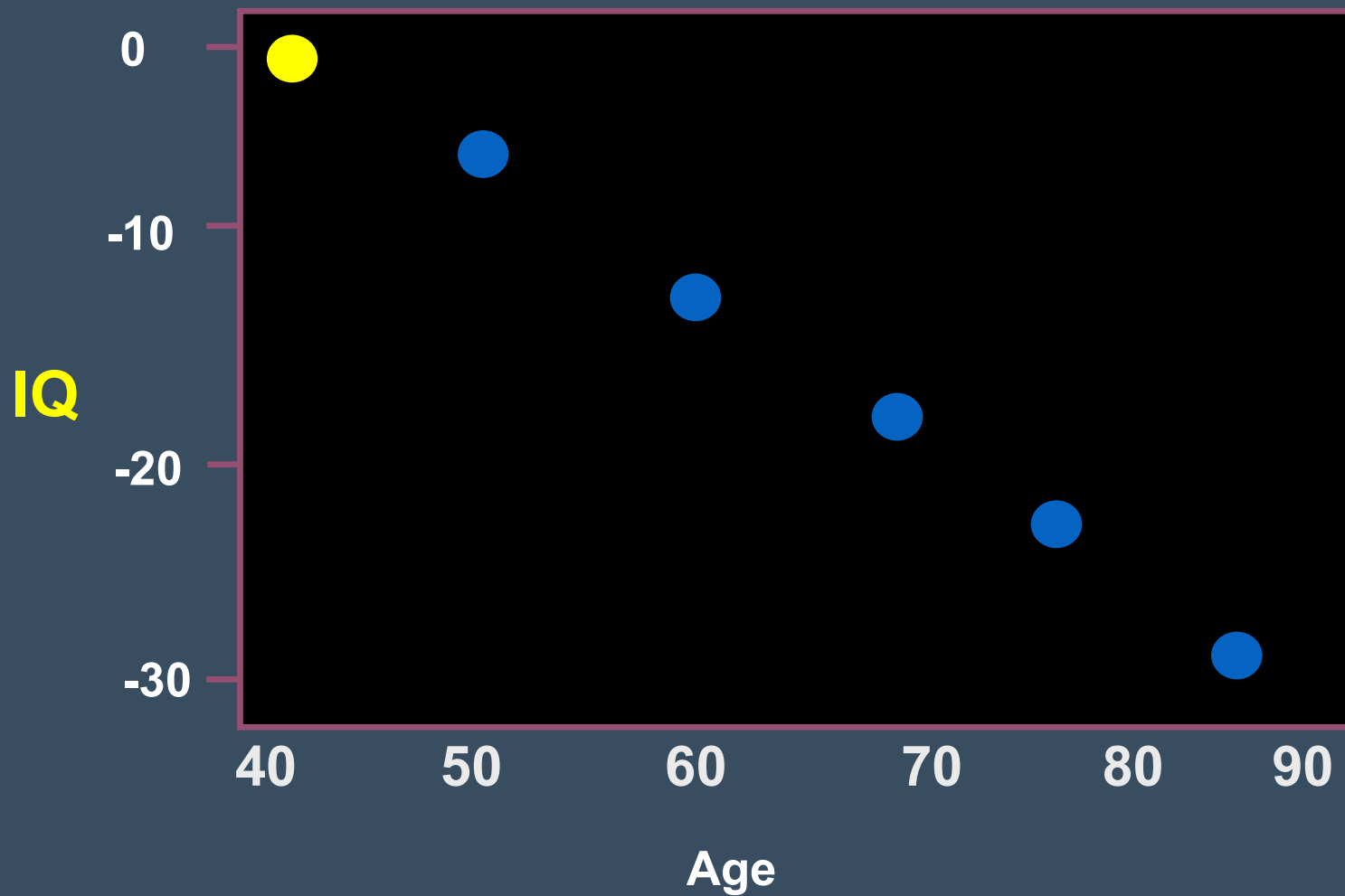
6

Get a coach

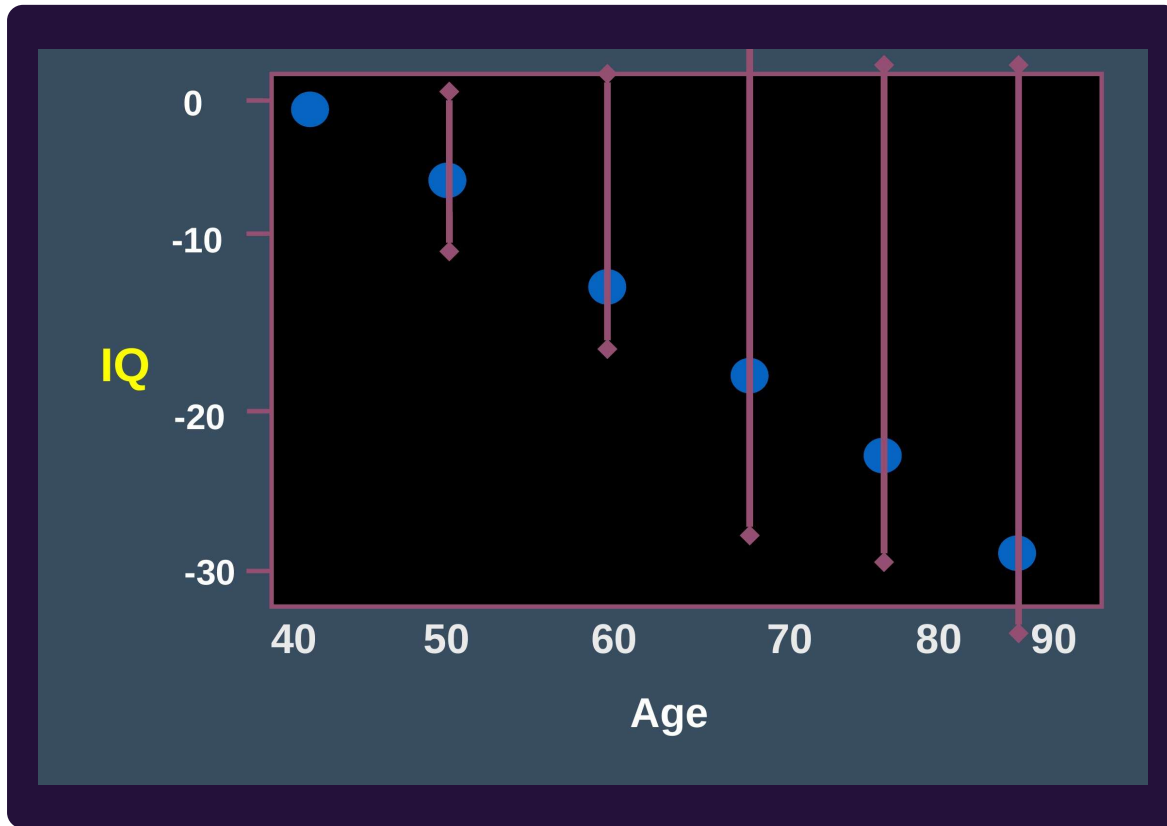
and just do it.



Harvard Physician



Cognitive Decline Is Common, Not Inevitable

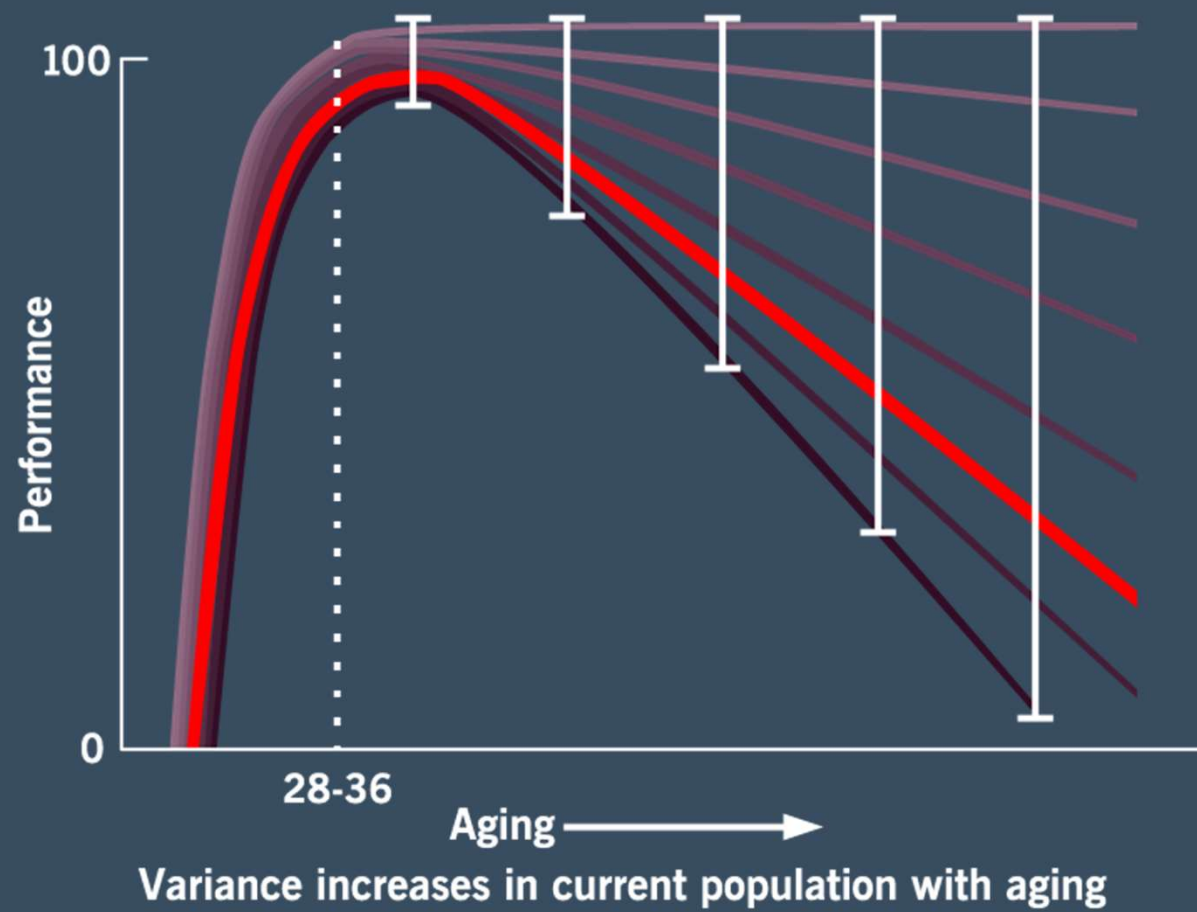


HARVARD PHYSICIANS: IQ CHANGE BY AGE

25%

do not lose IQ points as they age.

How do you become one of the 25% who do not lose IQ points as you age?



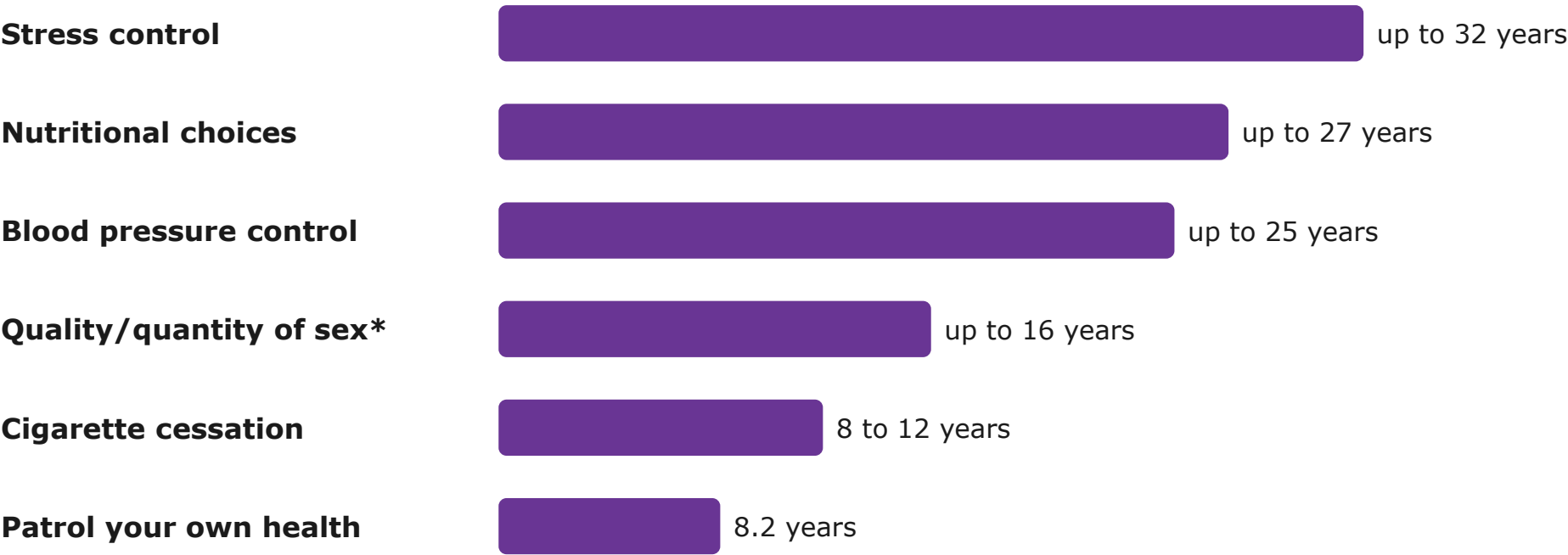
Wellness: Make Your *RealAge* Younger--risk of disability & death at age 58 if do average of all other choices

	Years Younger
✓ BP Control	up to 25 years
✓ Cigarette Cessation	8- 12 years
✓ Stress Control	up to 32 years
✓ Patrol Own Health	8.2 years
✓ Quality/Quantity of Sex*	up to 16 yrs
✓ Nutritional Choices	up to 27 years

* Mutually Monogamous--Excludes STD risk

Wellness: Make Your *RealAge* Younger

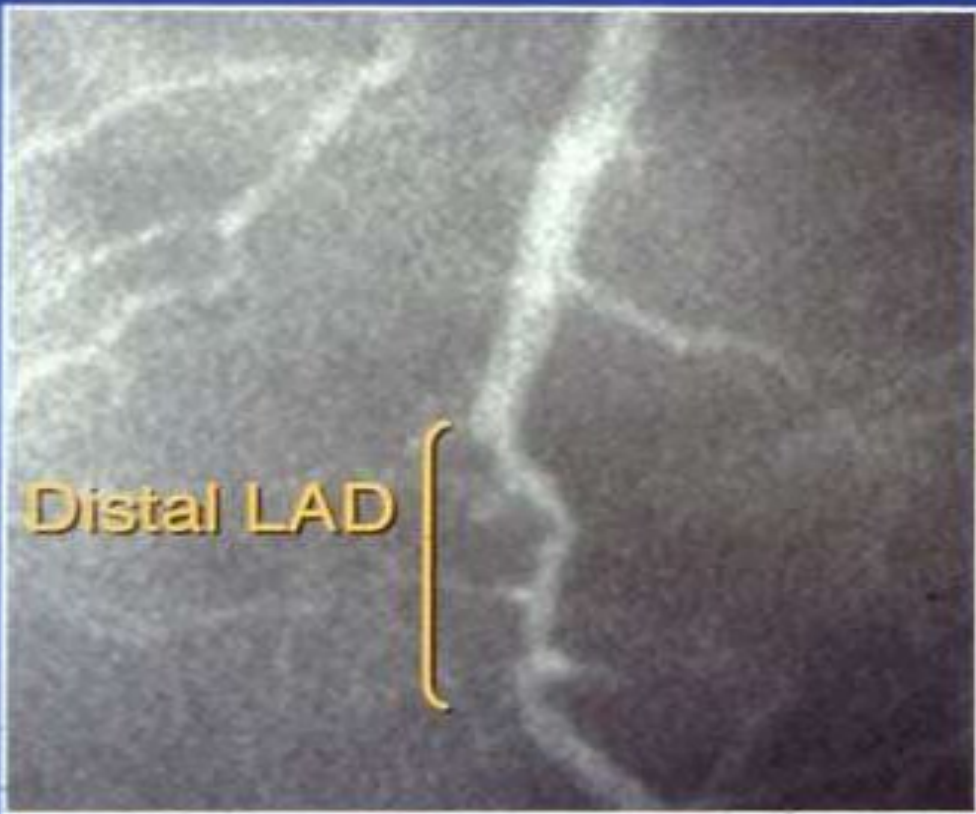
Years younger, at age 58, versus the average of all other choices



**Mutually monogamous; excludes STD risk.*

Reversal of Coronary Disease

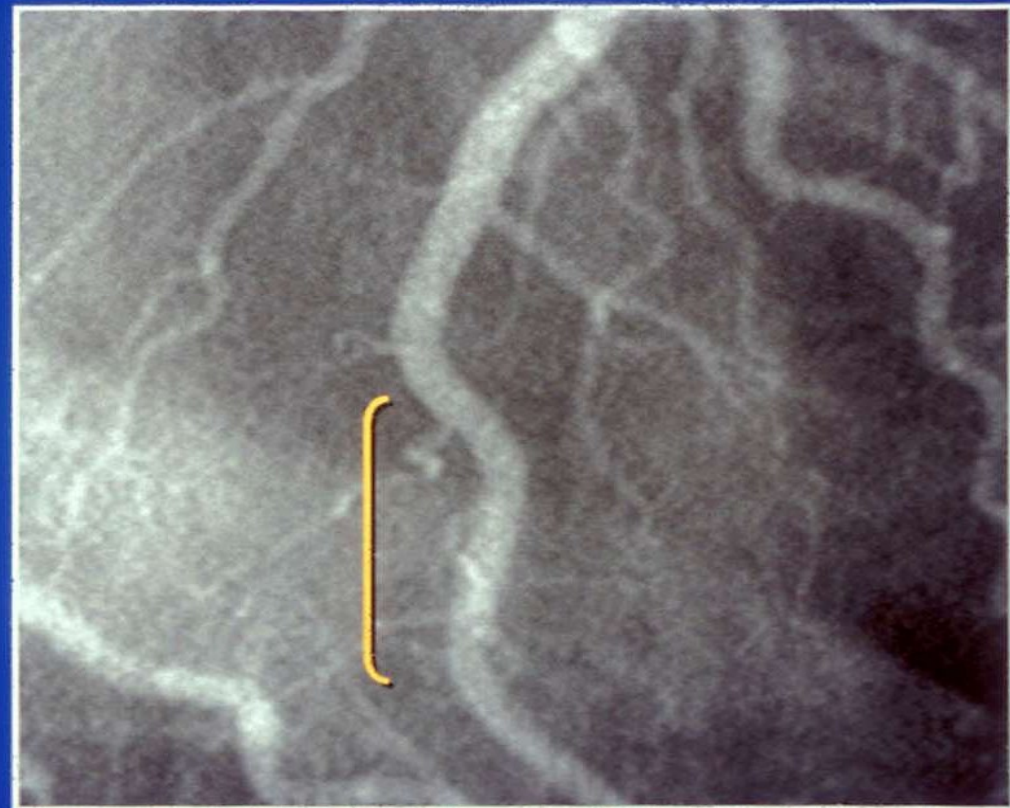
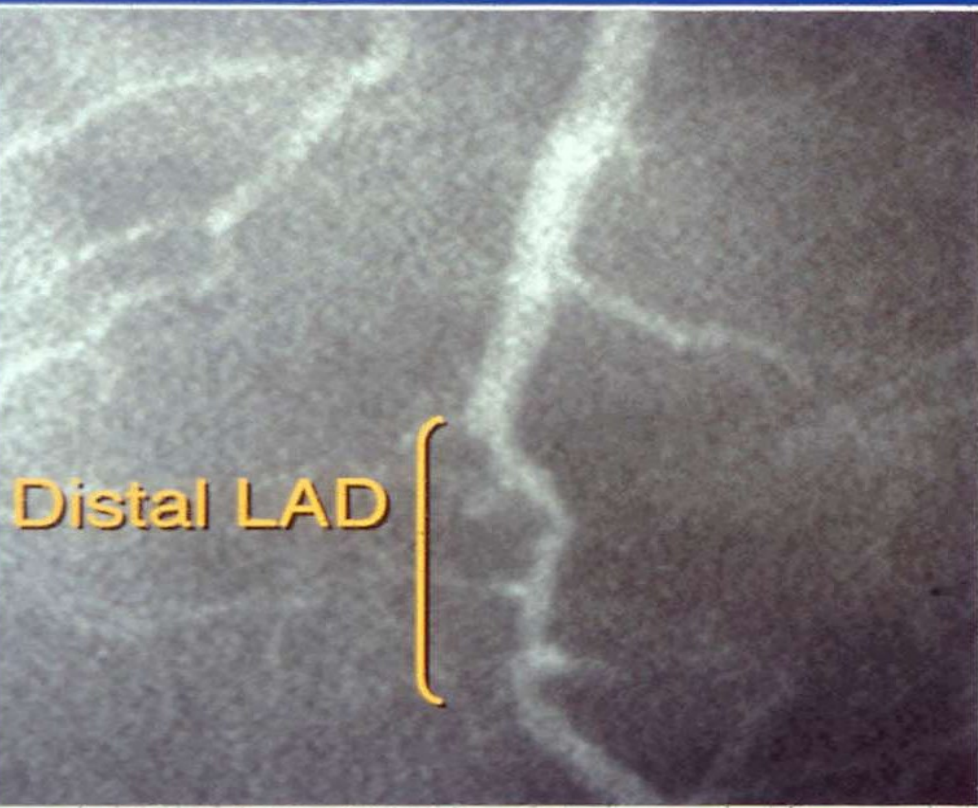
November 27, 1996



Reversal of Coronary Disease

November 27, 1996

July 22, 1999



The Human Genome Project: Your Choices Flip the Switches

300,000

genes expected, based on the amount of DNA in the nucleus

22,500

genes actually found

~1,500

genes on and producing proteins at any one time

80–93%

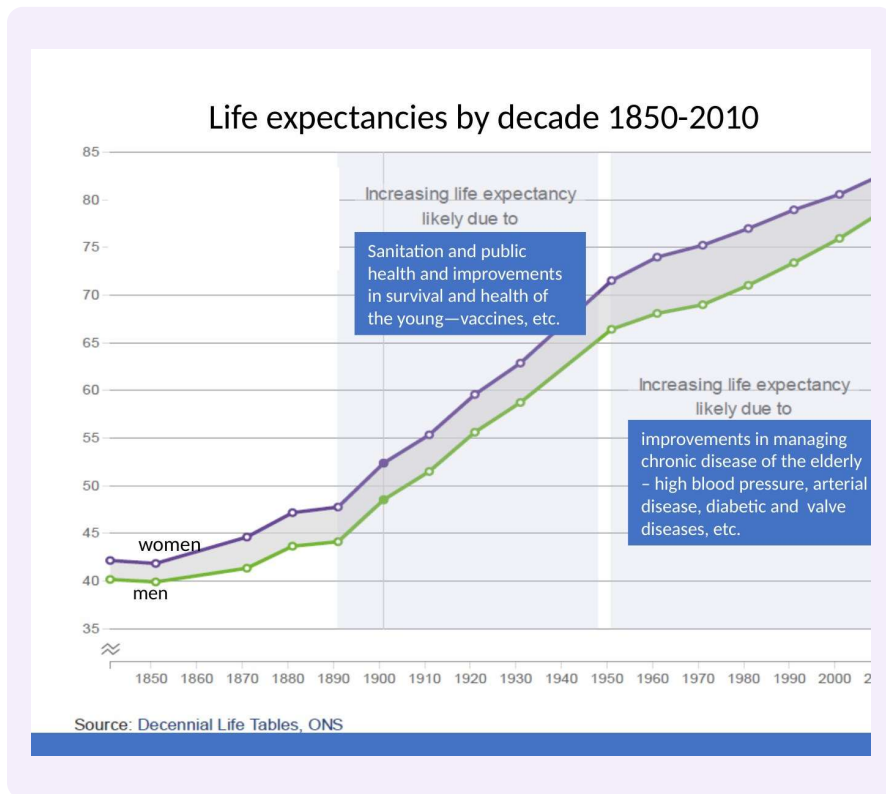
of which genes are on or off is controlled by your choices by age 18

What was the rest of the DNA? Seven years later it was found to be switches that control which of your genes are on and producing protein, and which are off.

Longevity Predictions:

Your approximate age in 2020	Average lifespan predicted for you when you were born (female*)	Average lifespan for those born in your year of birth in 2020	Predicted average lifespan for you in 2030 (Longevity Playbook Prediction)	Additional years for you to live as of 2023--
25	79	82	125	95
35	78	82	122	85
45	77	82	120	75
55	74	82	115	60
65	73	82	110	45
75	68	82	100	25
85	62	89	94	9

Life Expectancy: Linear to Exponential?



+2.5 years

per decade, on average, 1850 to 2020: linear

+30 years

in a single decade, 2023 to 2033, at least: exponential

"Ray Kurzweil told me in 2004 we'd know by 2033 if life expectancy could go exponential."

He was, and is, right on.

Life expectancy by decade, 1850–2020, women and men

What an Exponential Decade Means

30 steps

Thirty linear steps take you 30 yards. Thirty exponential steps take you 26 times around the earth.

9.3 → 2.3

Deaths per 1,000 per year: an unprecedented decline over a single decade, adding three decades of life.

19.2% → 12.8%

U.S. medical costs as a share of GDP, 2026 (expected) to 2050. This requires a change in behavior as well as in longevity and government policy.

Wellness Evolves Into Longevity

WELLNESS

Slowing Aging

Making your **RealAge** younger: reducing your risk of disability and death at any age, and changing your epigenes to keep your cells as young as possible.

LONGEVITY

Reversing Aging

Making your cells **YOUNger**, **YOUNgevity**, by reversing one or more of the mechanisms of aging.

Longevity the Next and Most Major Disruptor

...

The Opportunity of a Lifetime—to be 40 again when the Calendar says 90

**BUT YOU HAVE TO STAY YOUNG
TO GET YOUNGER**

Am I Too Early? Innovations Ahead of Their Time

1978

Stopped extra preoperative tests that do not matter. Now standard of care.

1979–80

Brought transesophageal echo into the OR. Now standard of care.

1980–86

Started prehab in cardiovascular patients to improve outcomes. Now standard of care.

1994–99

Developed the RealAge metric (NPV of health choices) to quantify biologic age and healthspan. Now the best estimate of disability and death risk.

1998–2000

First care guideline by multiple board specialties. Now standard of care.

1998–2002

Developed the cloud. A patent suit has now garnered my partner over \$1 billion (2024–25).

1999

RealAge book: #1 in 5 countries, displacing Harry Potter. Now called the “Father of Wellness.”

2005

Started an AI coaching program to keep Cleveland Clinic employees healthy: saves \$190M a year, \$1.5B over the last 11 years.

2008–17

Microbiome patent, still active worldwide.

2023–26

Started a TPE company to help **YOU** get younger now.

US 2004/0205055A1

(19) **United States**

(12) **Patent Application Publication**
Overton et al.

(10) **Pub. No.: US 2004/0205055 A1**

(43) **Pub. Date: Oct. 14, 2004**

(54) **SYSTEM AND METHOD FOR
ESTABLISHING AND RETRIEVING DATA
BASED ON GLOBAL INDICES**

(76) Inventors: **John Overton**, Chicago, IL (US);
Michael F. Rotzen, Chicago, IL (US)

Correspondence Address:

Joseph F. Hitz
BRINKS HOFER GILSON & LIONE
P.O. BOX 10395
CHICAGO, IL 60610 (US)

(21) Appl. No.: **10/646,350**
(22) Filed: **Aug. 22, 2003**

Related U.S. Application Data

(63) Continuation of application No. 10/102,179, filed on Mar. 19, 2002, now abandoned, which is a continuation of application No. 09/111,896, filed on Jul. 8, 1998, now abandoned, and which is a continuation-in-part of application No. PCT/US/98/00624, filed on Jan. 15, 1998.

Publication Classification

(51) **Int. Cl.⁷** **G06F 17/30**
(52) **U.S. Cl.** **707/3**

(57)

ABSTRACT

A system and method for establishing and retrieving data based upon global indices established on the date of first use by a user. The system uses a distributed data name service (DDNS) which uniquely identifies users of the system based upon the unique ID of devices on the system combined with the date and time of first use by the user. Both the unique device ID and the unique user ID's are stored on servers of the system. This unique user ID generated is used for all subsequent uses of the system by the user. Searching for data generated by devices of the system relating to a particular user is accomplished by searching for instances of the user ID on servers of the system rather than by searching for the data itself. A simplified data transport protocol allows for the transfer of data from one location to another after the data is located.

SDTP/DDNS
Network Topology Example

awarded to Overton from Amazon in April 2024 for infringement of the cloud patent

+ **\$500M more each** from Microsoft and Google

U.S. Patent Application Publication US 2004/0205055 A1 (Overton et al.), October 14, 2004



DISCLOSURE OF INTERESTS:





Entrevista com o médico americano
Michael Roizen, o papa do rejuvenescimento

Edição 408 - edição 1.000
ano 26 - nº 33 - R\$ 5,00
11 de junho de 2003

veja

www.veja.com.br

**RECEITAS
DA CIÊNCIA
PARA
MANTER-SE**

JOVEM

AOS 30, 40, 50... ...E 60 ANOS



FROM THE #1 NEW YORK TIMES BEST-SELLING

FROM THE #1 NEW YORK TIMES BEST-SELLING AUTHOR

FROM THE #1 NEW YORK TIMES BEST-SELLING

M

Please do PREORDER Thank you

HAEL F. ROIZEN,
TED GORDON, ESQ.

YO YOU YOU GETTING GETTING GETTING OLD OLDER OLDER



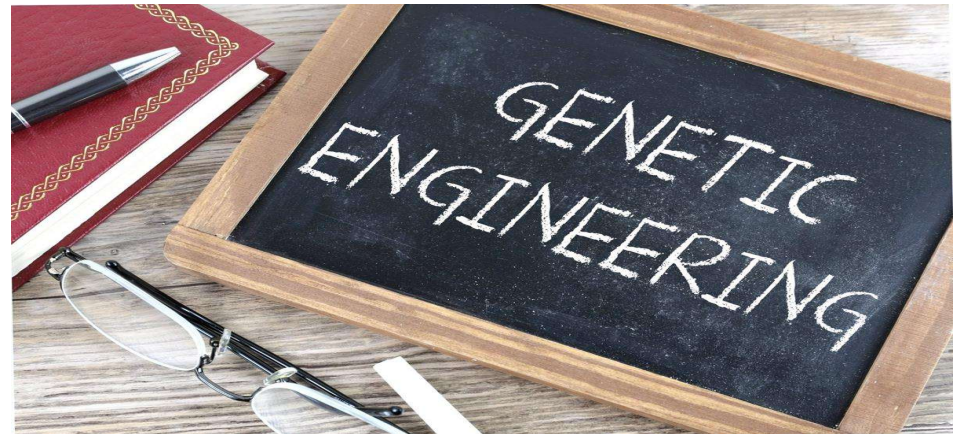
THE OWNER'S MANUAL
FOR YOUR GOLDEN YEARS

THE OWNER'S MANUAL
FOR YOUR GOLDEN YEARS

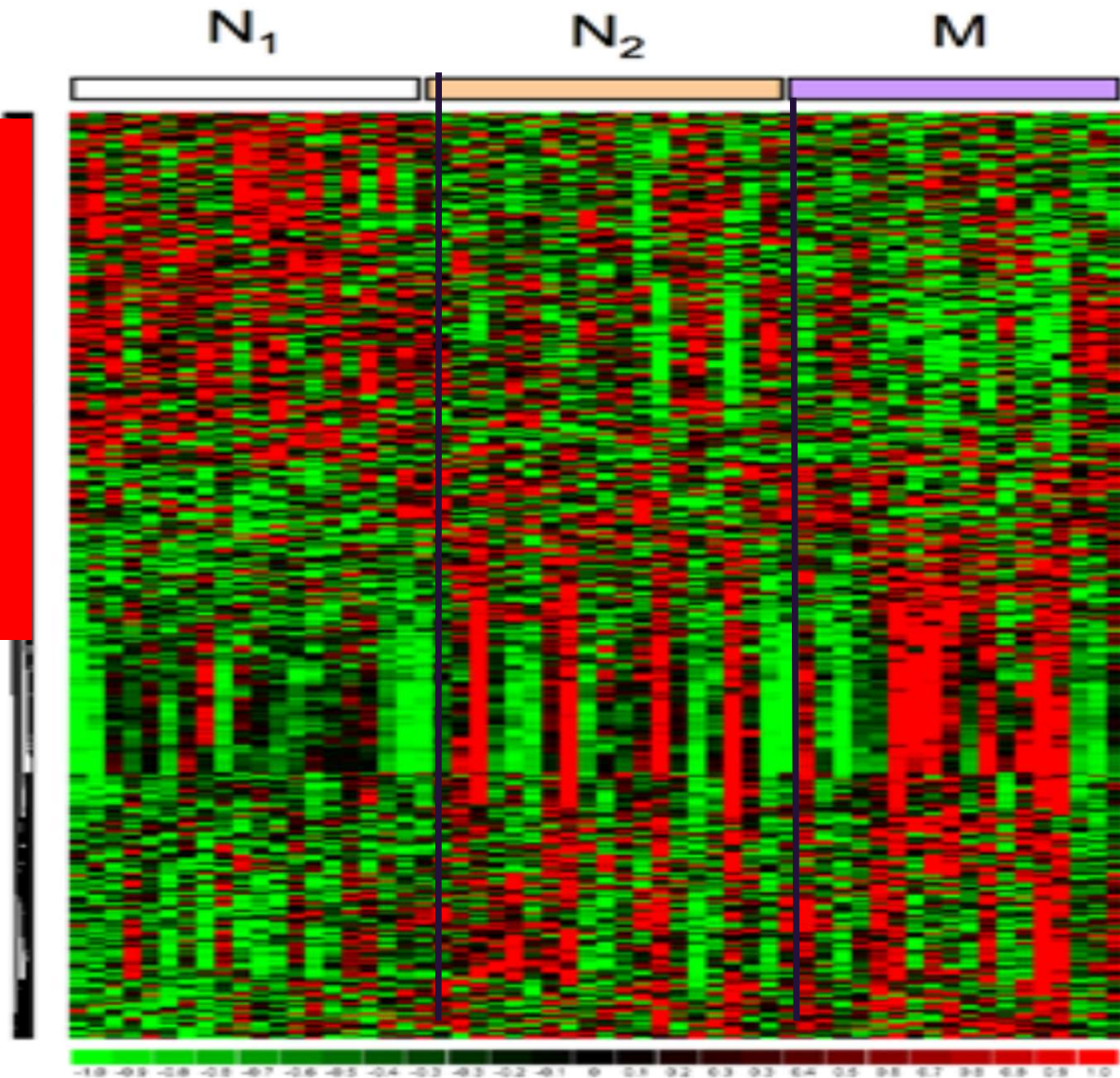
THE OWNER'S MANUAL
FOR YOUR GOLDEN YEARS

You Genes Make Your Proteins—Those Proteins Make You & Your Health etc.

- You Can Control Your Genes— That is Why You Can Have A Do-Over**



**Stress
Management
Changes
Which of Your
Genes Are On**



You Can Control Your Genetic Inheritance

All genes do is make proteins or watch other genes. Which are on or off is largely under YOUR control.

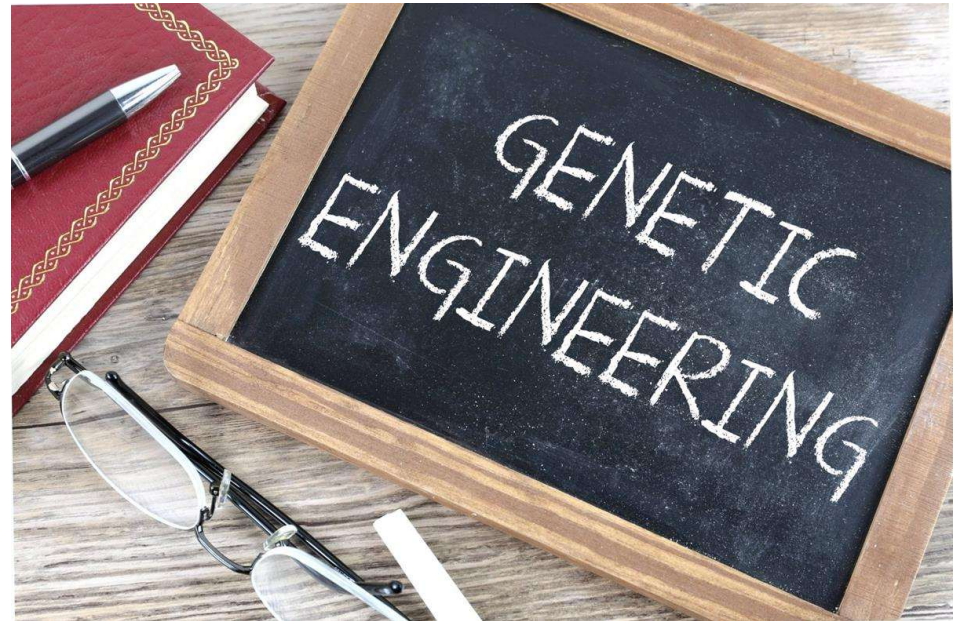


You are a genetic engineer for YOU.

Source: <https://doi.org/10.1016/j.neuron.2023.08.012>

You Can Control Your Genetic Inheritance

- You are a genetic engineer for **YOU**



**With 14 shots on goal, we think there is
a 80+% chance you can be 40 when
your calendar strikes 90--**

**But, you need to keep young to take
advantage of the advances.**

The “6 Normals + 2” Foster Sustained Health

1 Blood pressure

<140/<90; now <125/<85

2 Weight

BMI 21 to 29.9, or waist < ½ height

3 Blood sugar

FBS <107 or HbA1c <6.4; now <5.6; uric acid <5.0

4 LDL cholesterol

<130 or <100; now <70

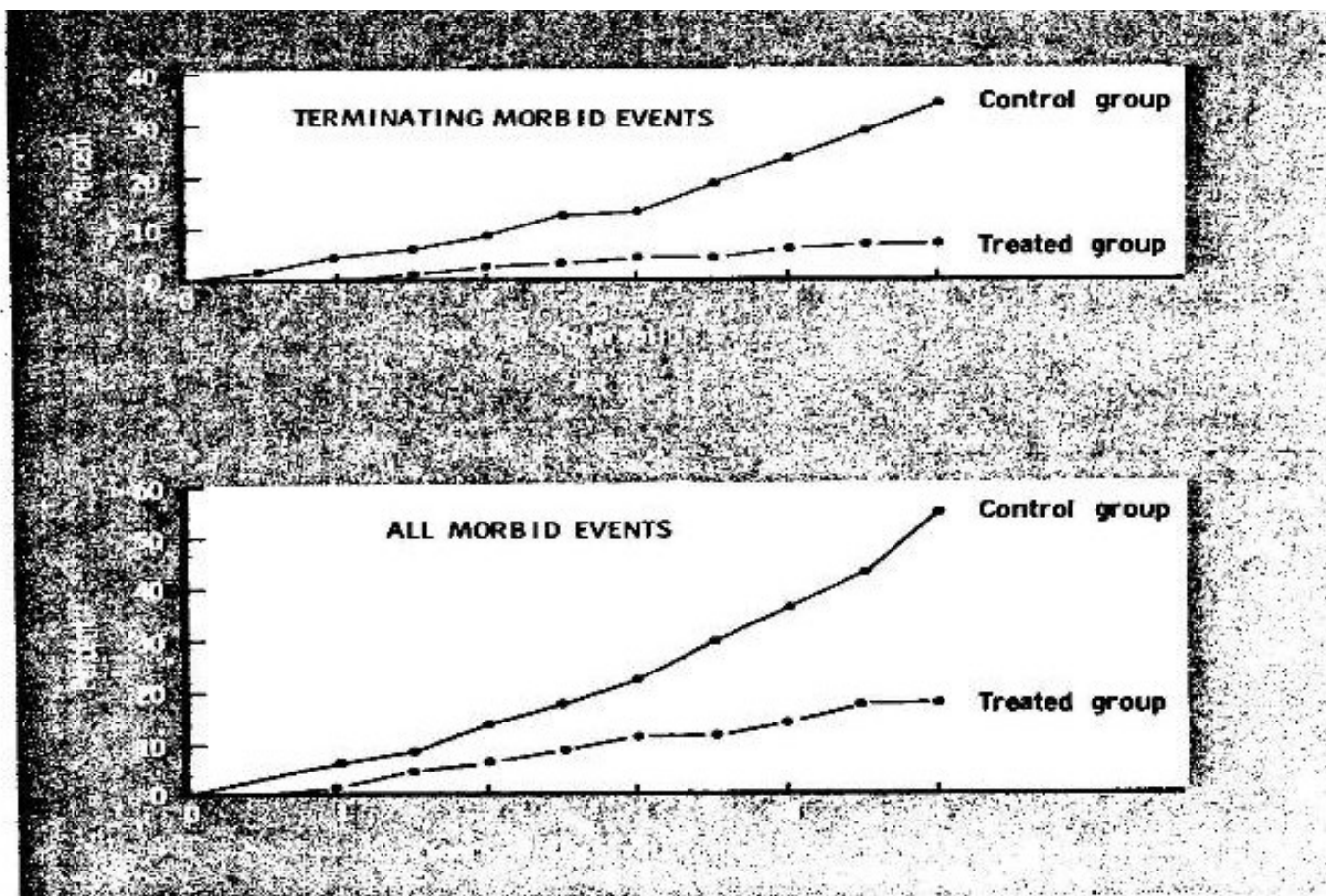
5 Tobacco

No cotinine in urine

6 Stress

Stress management program active

+2 See a primary care provider, and keep screenings and immunizations up to date.



2. Estimated cumulative incidence of morbidity over a five-year period as calculated by life-table method. Terminating morbid events (top) and all morbid events (bottom).

morbidity events were in the older age group. Of the 56 control patients developing morbidity events 41 were 50 years of age or older at the time

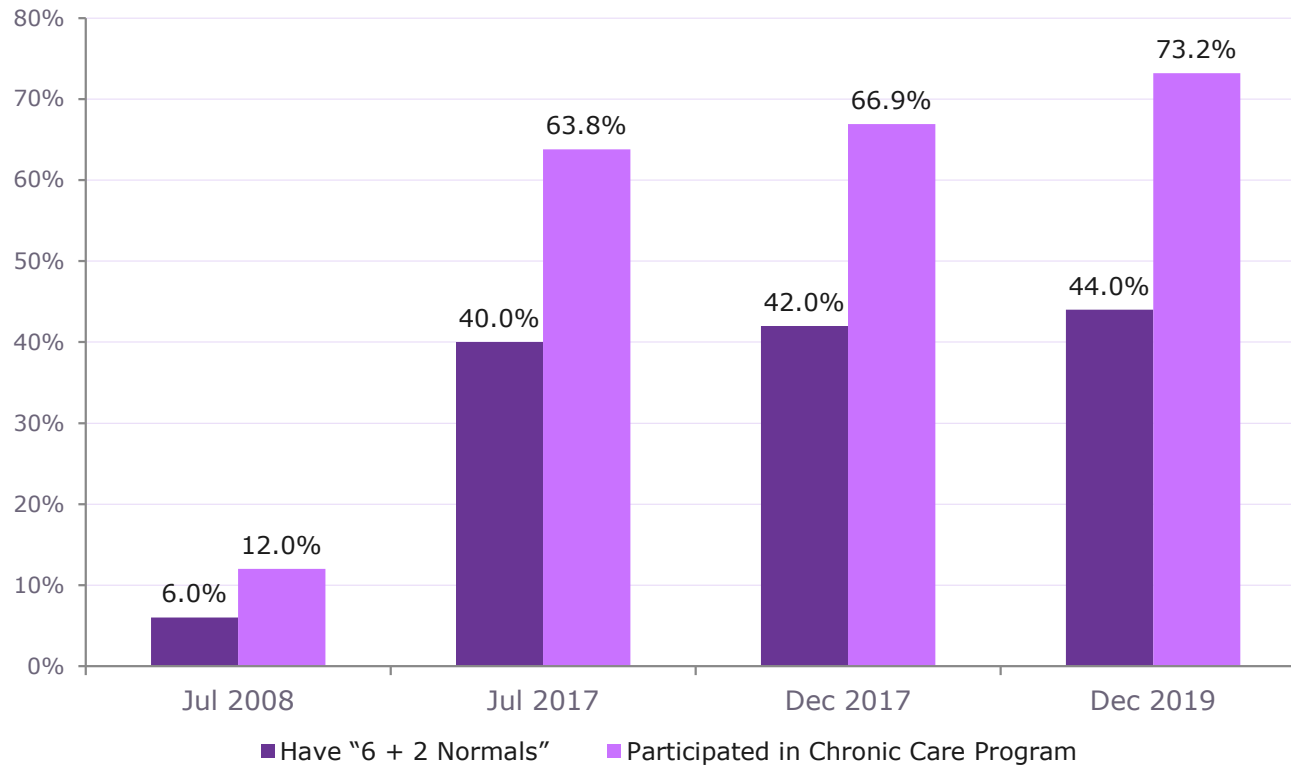
of morbidity events was no greater in Negro patients. In fact, in the control group the incidence of events was slightly lower in

morbidity. The two patients who were dropped from protocol because of drug-induced side effects have been described above. In addition, in the present report, those side effects requiring withdrawal of either reserpine or hydrochlorothiazide from the treatment regimen will be considered.

Administration of either reserpine or hydrochlorothiazide as placebo was withdrawn from the study because of side effect in 29 patients. In the reserpine and hydrochlorothiazide combined treatment group, the combined treatment was administered in tablet form. In order to avoid withdrawal from protocol because of side effect, presumably caused by one or both of the two agents, provision was made to permit substitution of a special tablet which contained either reserpine or hydrochlorothiazide and omitted the offending agent. These special tablets were made available on request of the participating physician. The appearance of the placebo tablet was made available for the control patients and the physician was to know whether the substituted tablet represented active drugs or placebo.

In the majority of the 29 patients, substitution of the special tablet was necessitated by pressor response, reserpine-induced side effect, or depression occurred in 11 patients. However, only seven of the 29 patients had been receiving the special drugs while the remaining 22 had been randomly selected

Cleveland Clinic: Reaching the “6 + 2 Normals”

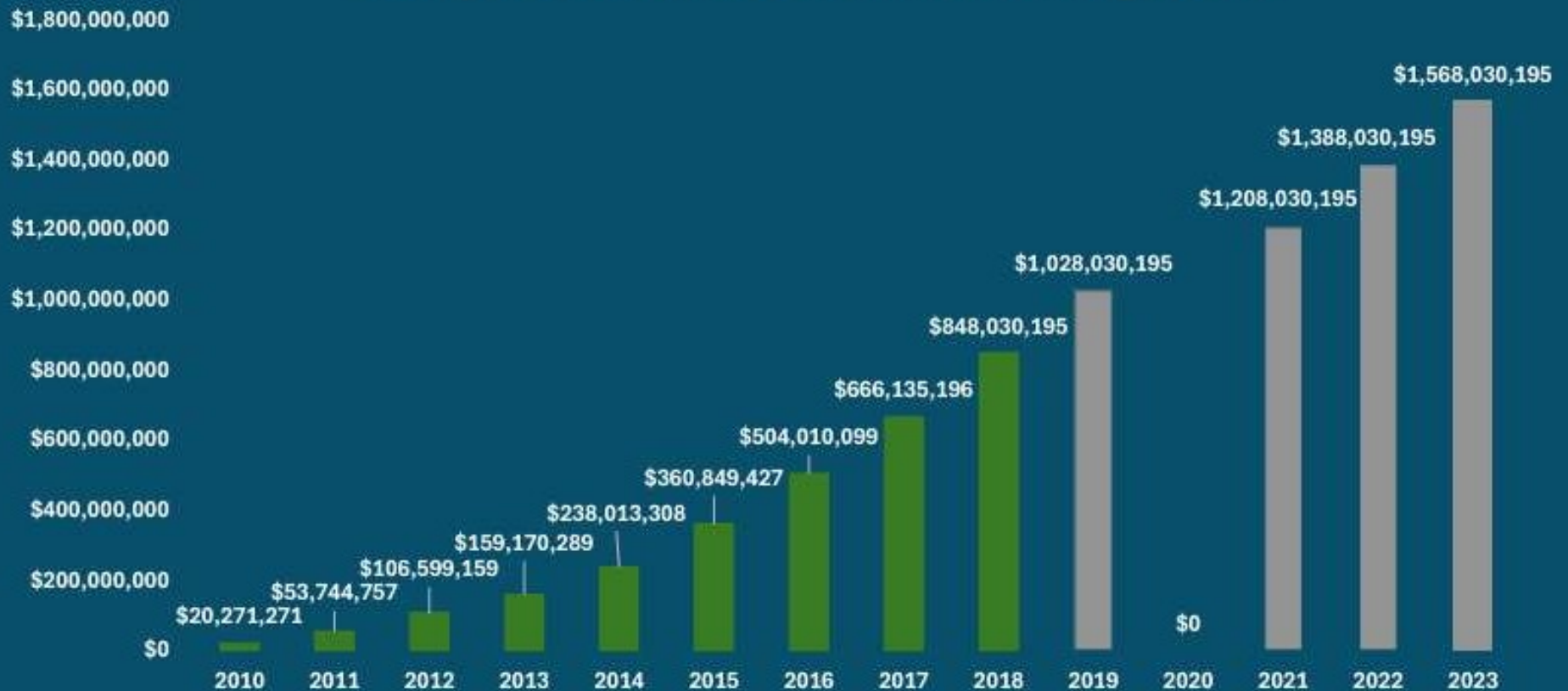


**6% →
44%+**

of employees and dependents reached all “6 + 2 Normals” between 2008 and 2019, as chronic care participation rose from 12% to 73%.

2017 and 2019 values are lower bounds (40+%, 42+%, 44+%).

Cumulative Annual Cost Avoidance Since 2010 Compared to National Commercial Average Trend



Source: EHP Financial Summary; claims paid through December, 2018

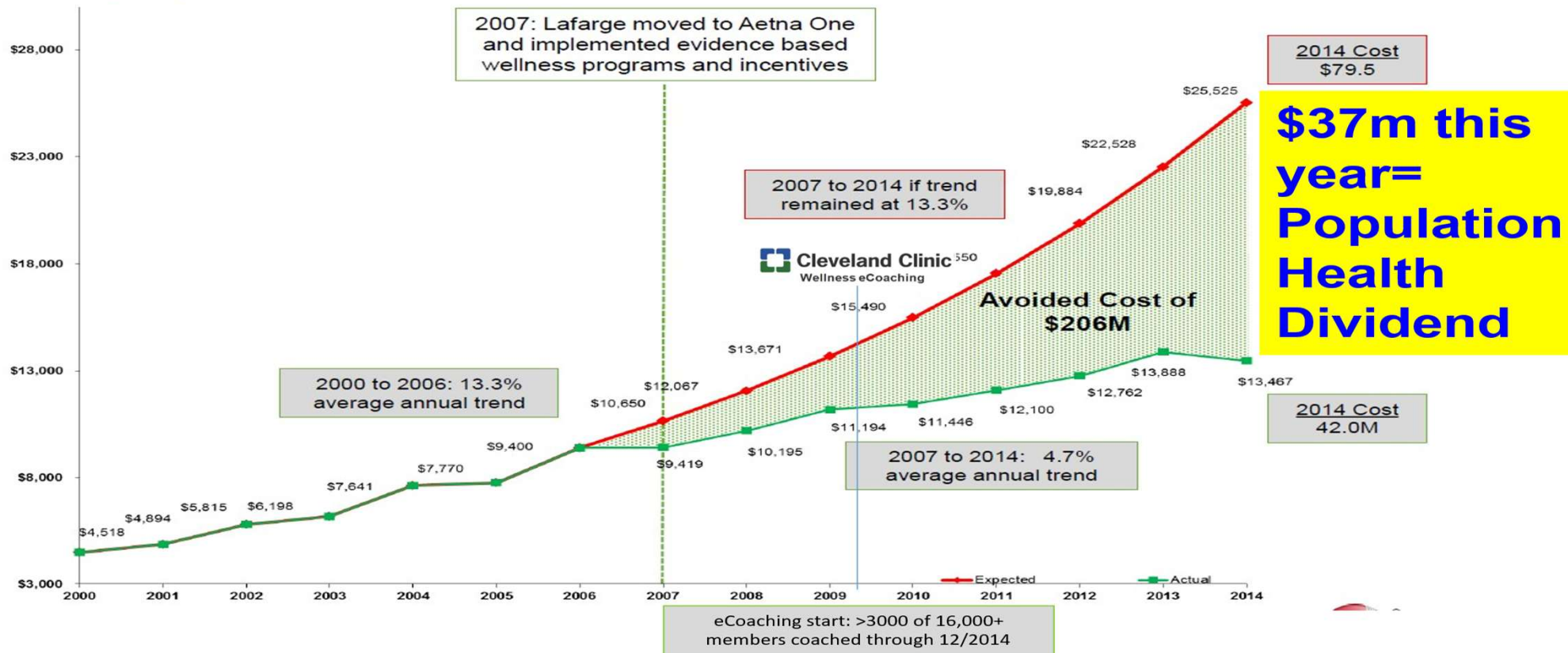
Annual National Trend based on Data from Health Care Cost Institute

Bars in Green are actual.

Bars in Grey are projected as we are no longer coaching but believe to be very conservative, but accurate.

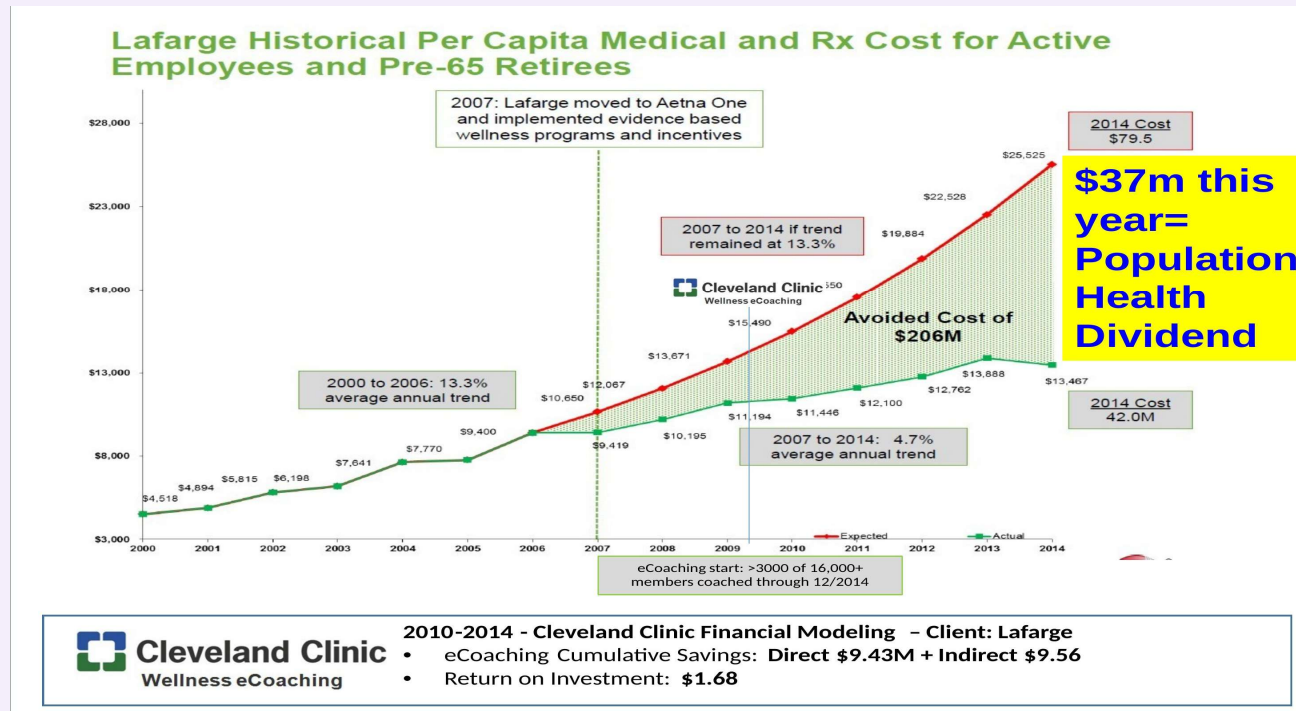
No increase in 2020 is projected due to COVID-19

Lafarge Historical Per Capita Medical and Rx Cost for Active Employees and Pre-65 Retirees



- 2010-2014 - Cleveland Clinic Financial Modeling – Client: Lafarge**
- eCoaching Cumulative Savings: Direct \$9.43M + Indirect \$9.56
 - Return on Investment: \$1.68

Lafarge: A \$37M Population Health Dividend



Lafarge historical per capita medical and Rx cost for active employees and pre-65 retirees; Cleveland Clinic financial modeling, 2010-2014

Coaching for Staying Healthy & Longevity

THE PROBLEM

**Coaching with humans
is expensive**

> \$50

per month, per person



THE SOLUTION

**An inexpensive AI coach
as a motivator**

Voice / phone

Text

Email

YOU: The World's First Longevity Care Plan

A personalized longevity journey in four simple steps

1

**Complete
assessment**

2

Get a care plan

3

Daily coaching

4

Track progress

\$1.5B

Healthcare costs saved

50+

Years of Dr. Roizen's
experience

12

Extra years disability-free

35%

Fewer sick days

18+ Interconnected Health Programs

Evidence-based protocols targeting every aspect of healthy aging

Physical Activity

"Want to feel 8 to 9 years younger? Move with purpose."

Nutrition & Timing

"You really are what you eat, and when you eat it."

Stress Management

"Stress ages you faster than almost anything else. Fight back."

Sleep Optimization

"For years, I undervalued sleep. But no more."

Blood Pressure

"If you focus on one number to stay younger, make it your blood pressure."

Weight Management

"If your waistline isn't where you want it, let's fix that the right way."

Menopause / Andropause

"Hormonal transitions aren't something you survive. You master them."

Cognitive Health

"What do we fear losing most as we age? Our minds."

Inflammation

"Inflammation is the silent fire behind nearly every major disease."

Muscle & Bone

"Muscle isn't just for bodybuilders. It's your best defense against aging."

Environmental Health

"You may not see it, but your environment is aging you."

Balance & Falls

"Falls threaten your independence, but they're preventable."

Supplements

"Supplements can help you stay younger, if you choose wisely."

Smoking Cessation

"If you smoke or vape, quitting is the single best thing you can do."

Eye Health

"The #1 cause of vision loss with age is macular degeneration. You don't have to lose your sight."

How It Works: Dr. Roizen's Proven Approach

A sustainable path to health transformation



SOAR + AI: Prevention & Recovery, Everywhere

Sustained Opportunity and Resilient Worthiness: for each person, with a job and with health

THE OPPORTUNITY · A job and good health: each one depends on the other

1 Each person needs a job they are fit for, to be healthy.

2 Each person needs to be healthy, to do a job well.

THE PROBLEM

Never enough practitioners

especially in rural areas, to help all people.

THE SOLUTION

Job aptitude placement + an AI coaching “nurse”

Tailored to each person’s environment, to help them get healthy, stay healthy and build a beneficial posse.

So each person can SOAR: with a job they are fit for, healthy for and proud of, and friends who form a beneficial posse.

This Can Change Everything

Personalized support for every person, at all times, in every community

1

A job, pride and health

A job, a feeling of pride and worthiness, and health, for each person.

2

Lower cost for government

Prevention saves public healthcare budgets substantial sums, reducing the cost of government.

3

A stronger economy

Happier people, lower government cost and a stronger climate for business.

SOAR + AI: Sustained Opportunity and Resilient Worthiness, with a job and with health

▶ SOAR + AI

Prevention & Recovery, Everywhere in Ohio

So each person can SOAR — with a job they are fit for, healthy for and proud of, and friends who form a beneficial posse.

Personalized support for every Ohioan — at all times, in every county.

Michael F. Roizen, MD

Prepared for Governor Mike DeWine · September 29, 2026

SOAR State of Ohio Adversity and Resilience

SOAR + AI Sustained Opportunity and Resilient Worthiness —
for each person, with a job and with health

Sustained health for each person, by feeling worthwhile to a community and to themselves.

► THE OPPORTUNITY

A job and good health — each one depends on the other.

1

Each person needs a job they are fit for
— to be healthy.

2

Each person needs to be healthy — to
do a job well.

THE PROBLEM

Never enough practitioners

in rural areas to help all people in Ohio.

THE SOLUTION

Job aptitude placement + an AI coaching “nurse”

Tailored to each person’s environment — to help them
get healthy, stay healthy and build a beneficial posse.

Personalized support for every Ohioan — at all times, in every county.

► PREVENTION & RECOVERY, EVERYWHERE IN OHIO

This can change everything in Ohio.

1

A job, pride and health

A job, a feeling of pride and worthiness, and health — for each Ohioan.

2

Lower cost for the state

Prevention saves Medicaid many dollars, reducing costs for state government.

3

A stronger Ohio

Happier people and less government cost — and Ohio continues its #1 ranking for business.

A great legacy from a great governor.

Personalized support for every Ohioan — at all times, in every county.

SOAR + AI Sustained Opportunity and Resilient Worthiness — for each Ohioan, with a job and with health.

14 Hot Areas of Exponentially Increasing Research that I wrote about in The Great Age Reboot, Some Are: **6 in humans now**

- Senolytics or **seno-rejuvenators --The Harvesting of Old Cells That Make Neighbors Old IN HUMAN TRIAL**
- Autophagy from 5 Day Calorie/Sugar/ Protein Restriction
- **Gene Editing with Immunomodulation IN HUMAN TRIAL**
- Immunologic Targeting
- **Stem Cells & Telomere Regeneration IN HUMAN TRIAL**
- **Proteostasis & Protein Inhibition TPE FITS HERE—AVAILABLE NOW**
- Mitochondrial Regeneration & Elimination of Obesity with Brown Fat From White Fat **GLP-1'S FIT HERE –AVAILABLE NOW**
- Microbiome Reprogramming & Photomodulation
- Bionic Bodies
- Induced Tissue Regeneration and **Epigenetic Reprogramming IN HUMAN TRIAL**

14 Shots on Goal: 6 Already in Humans

Hot areas of exponentially increasing research from The Great Age Reboot (selected)

Senolytics & senorejuvenators

Harvesting old cells that make their neighbors old

IN HUMAN TRIALS

Autophagy

From 5-day calorie, sugar and protein restriction

Gene editing with immunomodulation

IN HUMAN TRIALS

Immunologic targeting

Stem cells & telomere regeneration

IN HUMAN TRIALS

Proteostasis & protein inhibition

TPE fits here

AVAILABLE NOW

Mitochondrial regeneration

Eliminating obesity by turning white fat brown. GLP-1s fit here

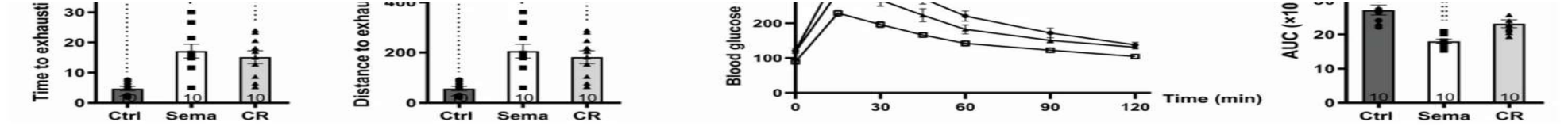
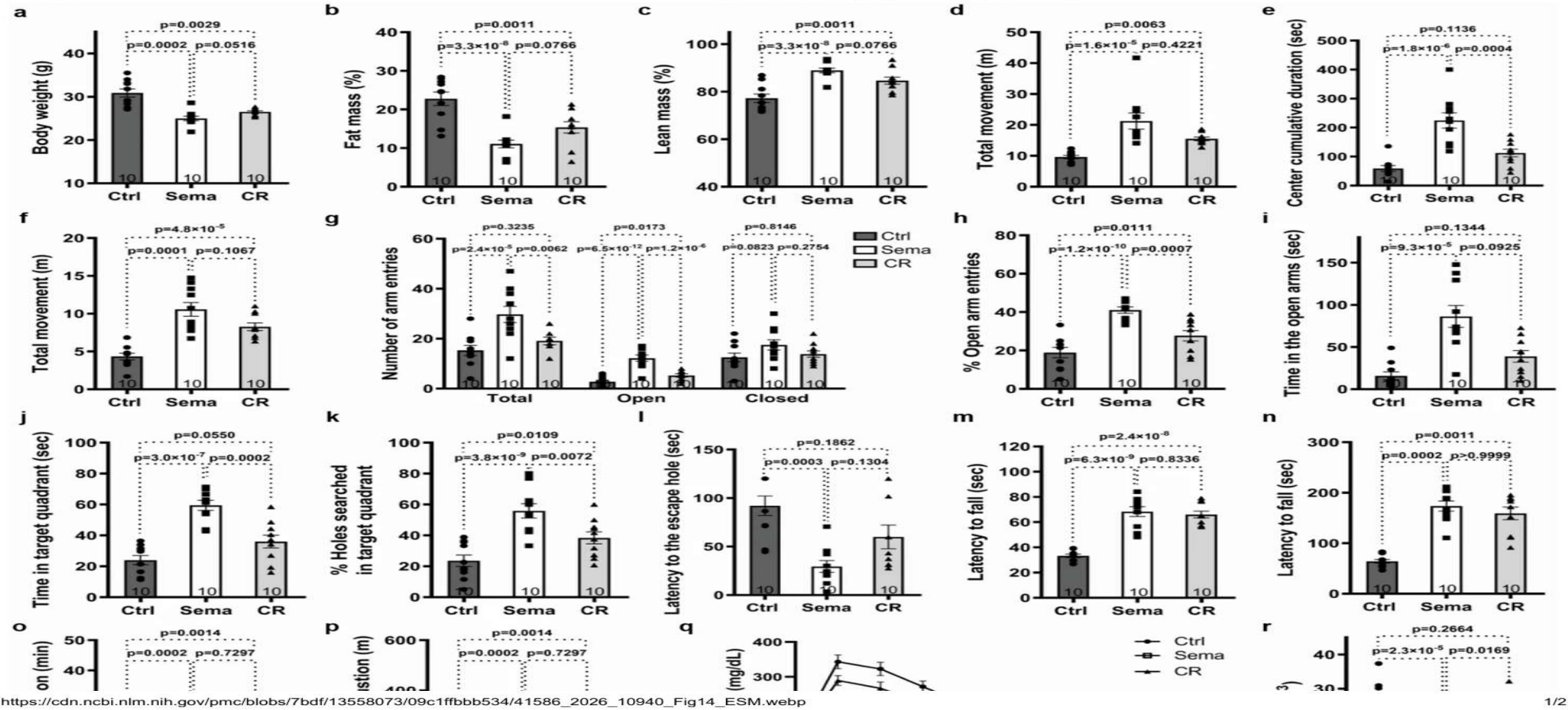
AVAILABLE NOW

Microbiome reprogramming & photomodulation

Bionic bodies

Induced tissue regeneration & epigenetic reprogramming

IN HUMAN TRIALS



Criteria for Specific Supplements and Small Molecules:

1. Vit D2/3 + K2
2. Multi
3. DHA/EPA-Omega-3
4. Ca⁺⁺/Mg⁺⁺
5. Statin
6. GLP-1-GIP-? Other Peptides
7. ASU
8. CoQ10
9. Collagen/Gelatin/
10. Creatine
11. Tumeric with piperine
12. Baby Aspirin 2x as day
13. Spermadine
14. Specific Probiotics
15. Bovine Colostum
16. Fiber/ SCFA
17. Colchicine
18. PDE5-I

Benefit Consistently Greater than Risk

- for typical man and /or woman over age 50 as shown by
- Peer reviewed studies in humans–
 - At least two RCT's (by at least two different groups) with dose curve, or
 - one RCT and more than one epidemiology study , or
 - multiple epidemiology studies by different groups
- Ability to determine from data disability or ACMortality rates
- With vote on the risk/benefit ratio by at least a 2/3rds vote by quorum of 9 member SAB of 4YOUngevity.com

Criteria for Specific Supplements and Small Molecules

18 CANDIDATES

Vitamin D2/3 + K2	Multivitamin	DHA/EPA omega-3
Calcium / magnesium	Statin	GLP-1/GIP & other peptides
ASU	CoQ10	Collagen / gelatin
Creatine	Turmeric with piperine	Baby aspirin, 2x a day
Spermidine	Specific probiotics	Bovine colostrum
Fiber / SCFA	Colchicine	PDE5 inhibitor

Benefit consistently greater than risk

for a typical man or woman over age 50, as shown by peer-reviewed studies in humans:

- At least two RCTs, by at least two different groups, with a dose curve; or
- One RCT and more than one epidemiology study; or
- Multiple epidemiology studies by different groups
- Data allow disability or all-cause mortality rates to be determined
- Approved by at least a two-thirds vote of a quorum of the 9-member 4YOUngevity.com Scientific Advisory Board

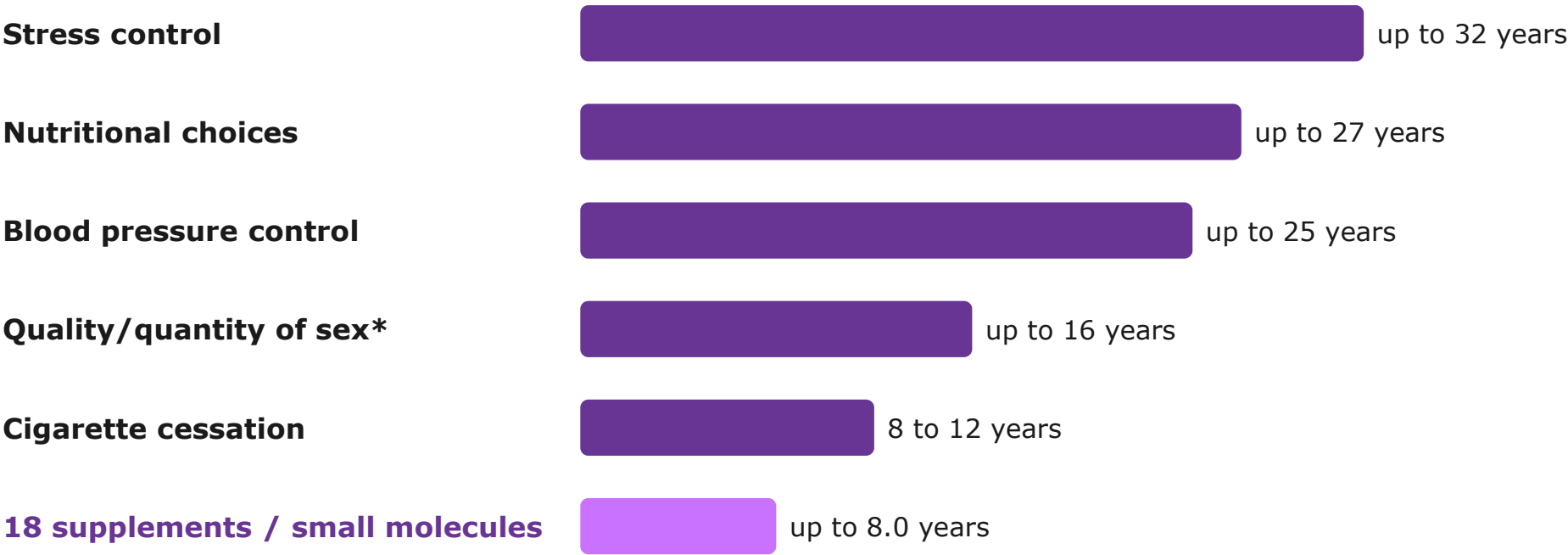
Wellness: Make Your *RealAge* Younger--risk of disability & death at age 58 if do average of all other choices

	Years Younger
✓ BP Control	up to 25 years
✓ Cigarette Cessation	8- 12 years
✓ Stress Control	up to 32 years
✓ 18 Supmts/Small Molec	up to 8.0 years
✓ Quality/Quantity of Sex*	up to 16 yrs
✓ Nutritional Choices	up to 27 years

* Mutually Monogamous--Excludes STD risk

Supplements & Small Molecules: All Together Only Up to 8 More Years

RealAge years younger, at age 58, versus the average of all other choices



**Mutually monogamous; excludes STD risk.*

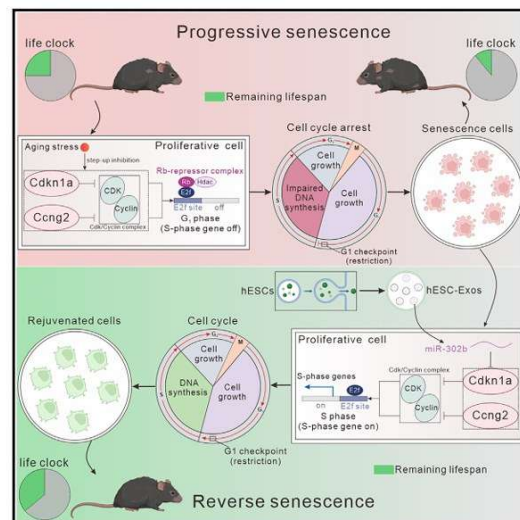
Seno-Rejuvenation: Reversing Senescent Cells

Cell Metabolism

Article

Exosomal miR-302b rejuvenates aging mice by reversing the proliferative arrest of senescent cells

Graphical abstract



Authors

Youkun Bi, Xinlong Qiao, Zhaokui Cai, ..., Hongjin Wu, Yuanchao Xue, Guangju Ji

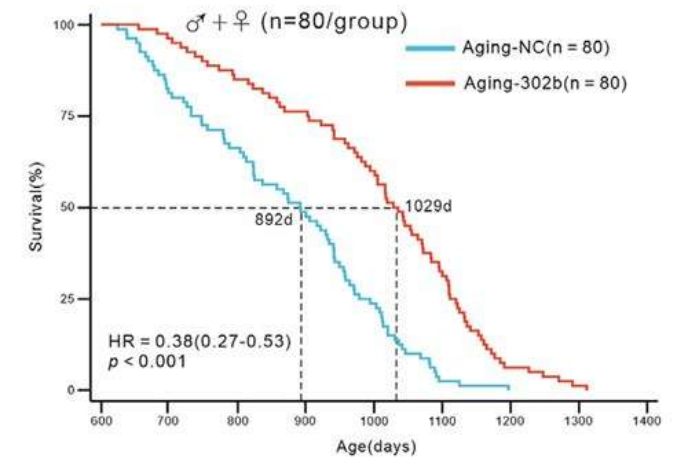
Correspondence

bao766@shutcm.edu.cn (H.W.), ycxue@ibp.ac.cn (Y.X.), gj28@ibp.ac.cn (G.J.)

In brief

Bi et al. propose the Senoreverse anti-aging strategy, which aims to reverse the proliferative arrest of senescent cells. Exosomal miR-302b is identified as a Senoreverse candidate that targets the cell cycle inhibitors *Cdkn1a* and *Ccng2*, rejuvenating aging mice by improving physical and cognitive functions, extending lifespan, and exhibiting no safety concerns throughout a 24-month observation period.

C



Bi et al., *Cell Metabolism*: exosomal miR-302b rejuvenates aging mice by reversing the proliferative arrest of senescent cells

Longevity: A Great Age Reboot Is Likely

14 shots on goal for reversing aging mechanisms fall into 4 (maybe 5) parts

1

Gene editing

Edit out chronic and devastating disease

2

Seno-rejuvenators

Turn old cells into young cells

3

Stem cell repair

Lengthen telomeres on stem cells so they can repair injuries

4

Repair signals

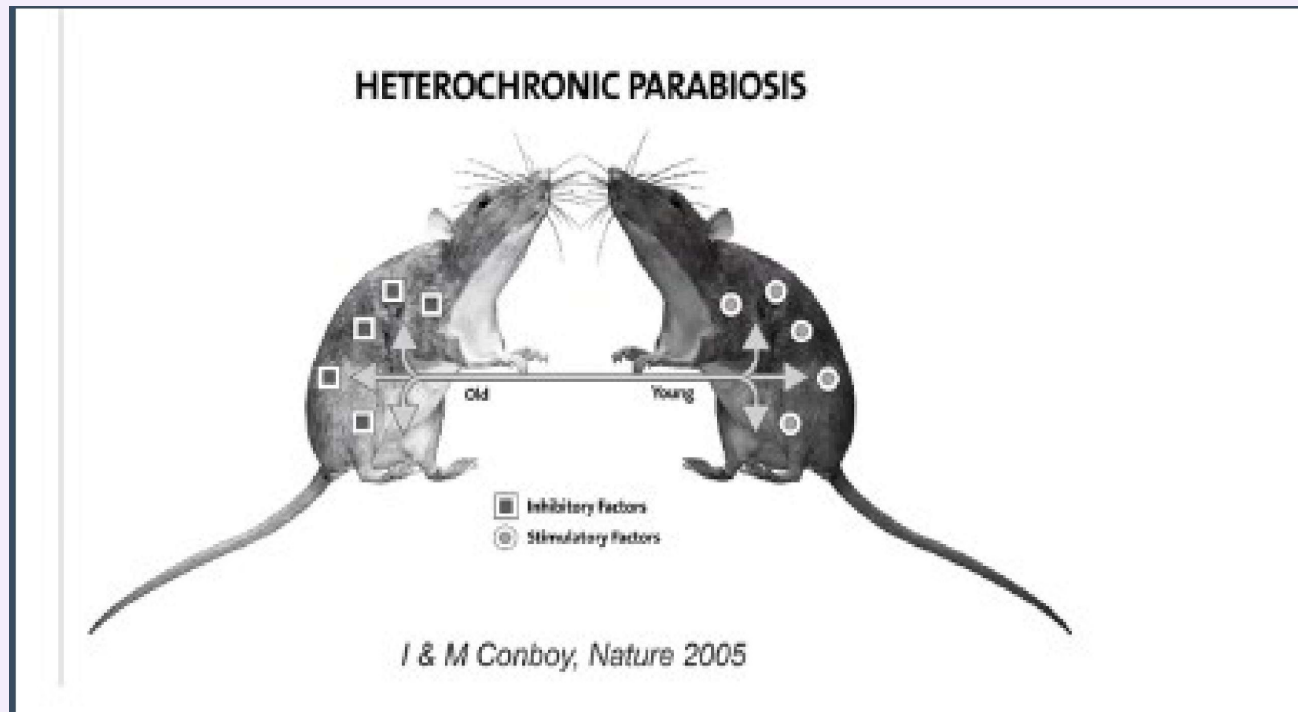
Get rid of old proteins

5

Maybe: sugar handling

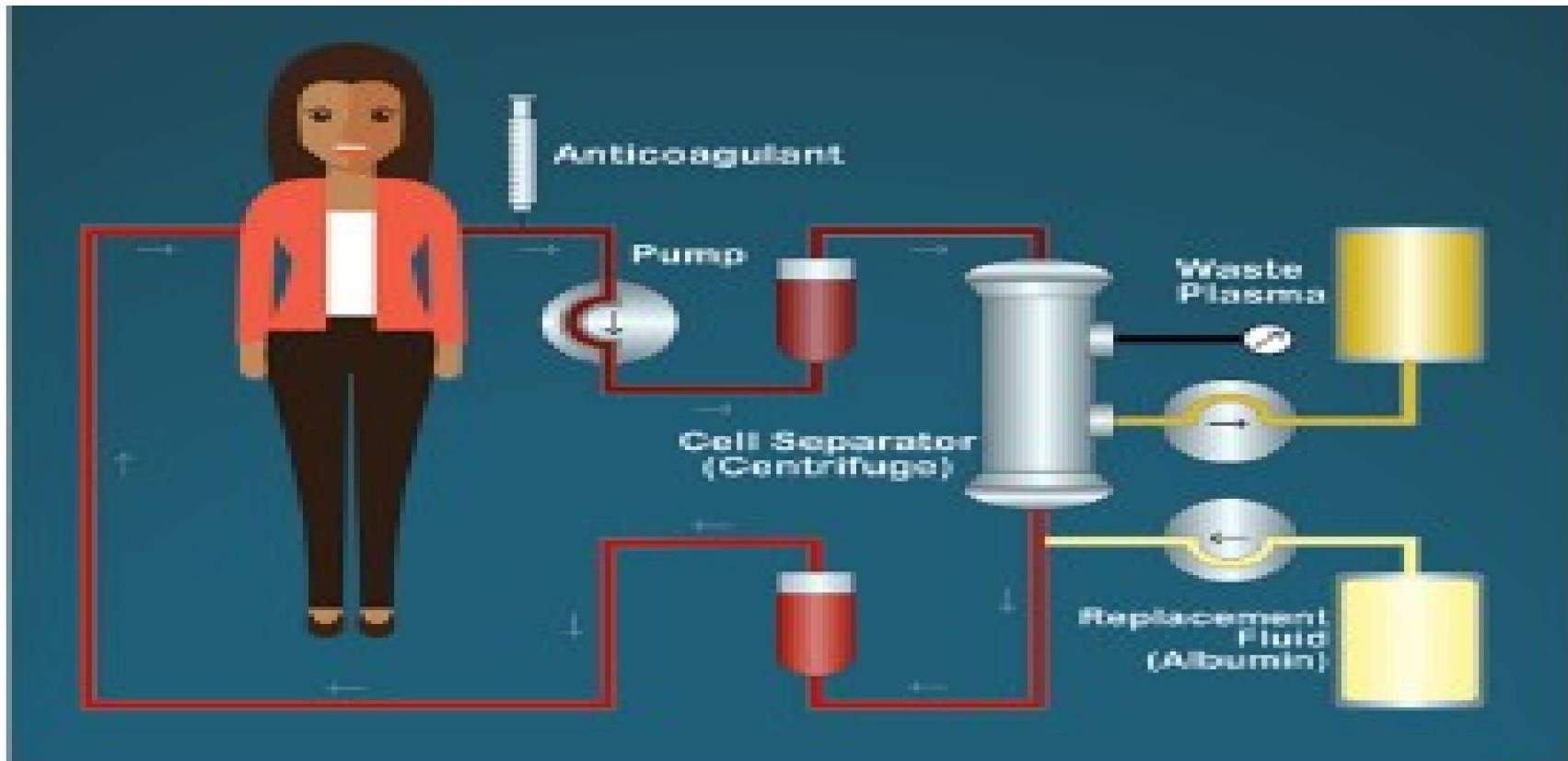
Change how we handle sugars

Heterochronic Parabiosis: Young Blood, Old Blood



I. & M. Conboy, Nature 2005

Therapeutic Plasma Exchange (TPE): How It Works



The AMBAR Trial: Plasma Exchange in Alzheimer's Disease

Received: 12 March 2021 | Revised: 2 July 2021 | Accepted: 11 August 2021

DOI: 10.1002/alz.12477

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

FEATURED ARTICLE

Neuropsychological, neuropsychiatric, and quality-of-life assessments in Alzheimer's disease patients treated with plasma exchange with albumin replacement from the randomized AMBAR study

Mercè Boada^{1,2} | Oscar L. López³ | Javier Olazarán^{4,5} | Laura Núñez⁶ |
Michael Pfeffer⁷ | Orlando Puente⁸ | Gerard Piñol-Ripoll⁹ | José E. Gámez¹⁰ |
Fernando Anaya¹¹ | Dobri Kiprova¹² | Montserrat Alegret¹ | Carlota Grifols⁶ |
Miquel Barceló⁶ | Jordi Bozzo⁶ | Zbigniew M. Szczepiorkowski^{13,14} |
Antonio Páez⁶  | the AMBAR Trial Group[#]

Boada et al., *Alzheimer's & Dementia*, 2021

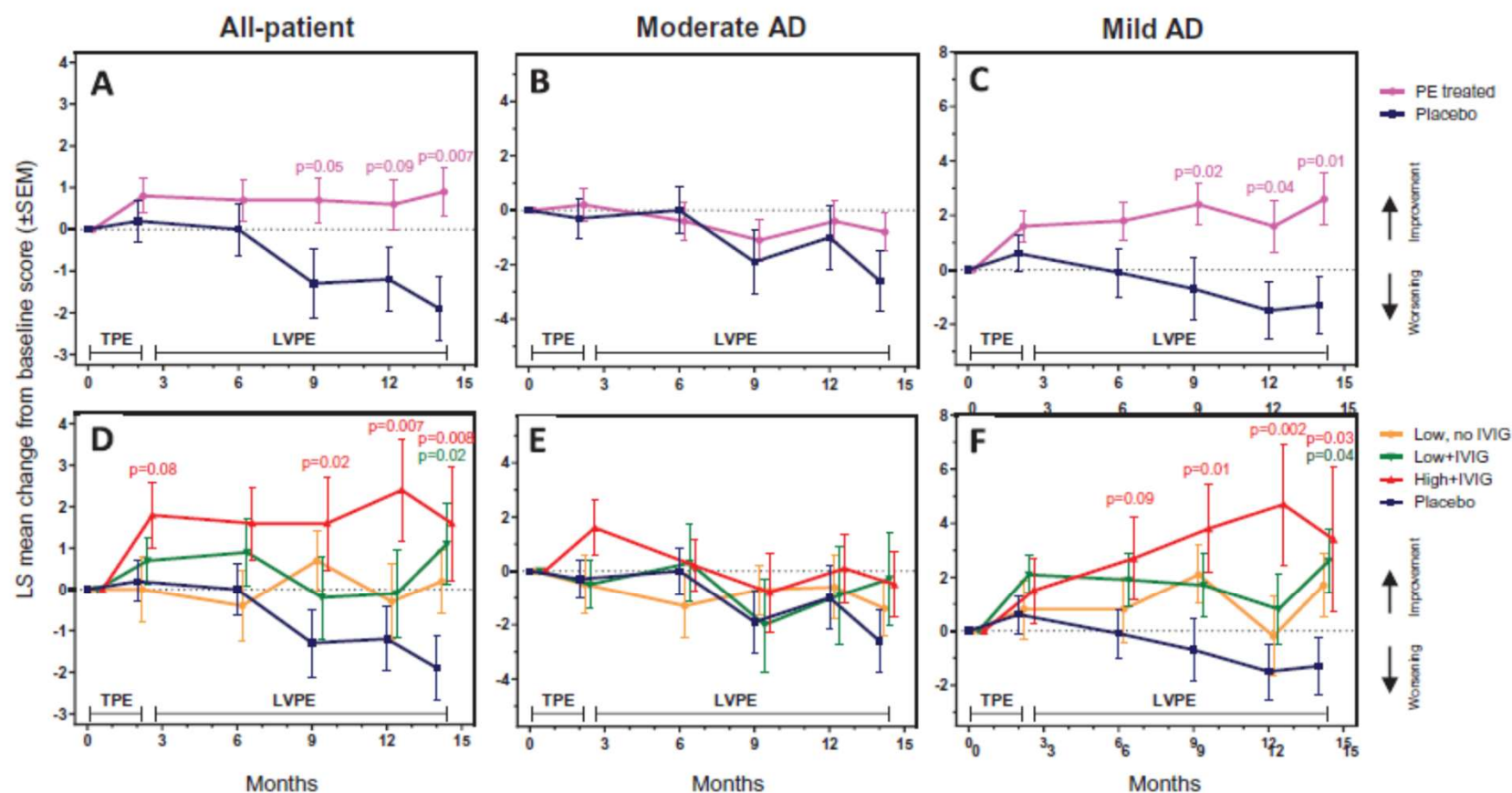


FIGURE 3 Phonetic Verbal Fluency test (PVF) scores in Alzheimer's disease (AD) patients (all-patient [panels A, D], moderate AD [panels B, E], and mild AD [panels C, F] populations) treated with plasma exchange (PE) with albumin replacement. TPE denotes the 2-month period of conventional therapeutic PE; LVPE denotes the 12-month period of low-volume PE. Statistical significance ($P < .05$) and borderline significance

AMBAR vs. Anti-Amyloid Antibodies: Effect Size

Table 1: AD Treatment Pipeline: Efficacy results of mAbs anti-Aβ and AMBAR

Effect size comparison across outcomes - % effect size is largest for AMBAR

	N	Alzheimer's treatment candidates			
		ADCS-ADL Effect Size	ADAS-Cog Effect Size	CDR-Sb Effect Size	ARIAs
mAb anti-Aβ	Aducanumab ENGAGE	1647	18%	11%	-2%
	Aducanumab EMERGE (10mg/kg)	1638	40%	27%	22%
	Lecanemab (BAN2401)	1795	37%	26%	27%
MULTI-MoA	AMBAR	347	52%	66%	71%

Efficacy comparative Table elaborated by the authors



ADCS-ADL: Alzheimer's Disease Corporative Study-Activities of Daily Living; ADAS-Cog: Alzheimer's Disease Assessment ScaleCognitive subscale; CDR-Sb: Clinical Dementia Rating-Sum of bones

United Prime Publications LLC., <https://acmcasereport.org/>

2

AD treatment pipeline: efficacy of anti-amyloid mAbs and AMBAR. The percent effect size is largest for AMBAR.

Table 1: AD Treatment Pipeline: Efficacy results of mAbs anti-Aβ and AMBAR

Effect size comparison across outcomes - % effect size is largest for AMBAR

		N	ADCS-ADL Effect Size	ADAS-Cog Effect Size	CDR-Sb Effect Size	ARIAs
Alzheimer's treatment candidates						
mAb anti-Aβ	Aducumumab ENGAGE	1647	18%	11%	-2%	40%
	Aducumumab EMERGE (10mg/kg)	1638	40%	27%	22%	
	Lecanemab (BAN2401)	1795	37%	26%	27%	12%
MULTI-MoA	AMBAR	347	52%	66%	71%	0%

Efficacy comparative Table elaborated by the authors



ADCS-ADL: Alzheimer's Disease Cooperative Study-Activities of Daily Living; ADAS-Cog: Alzheimer's Disease Assessment Scale Cognitive subscale; CDR-Sb: Clinical Dementia Rating-Sum of boxes

TPE Slows Cognitive Decline

Taragano et al.

9

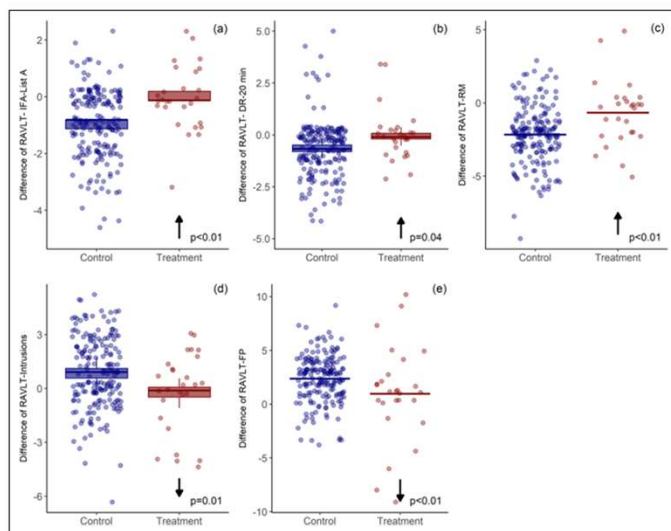


Figure 3. Memory test outcomes. Model-derived estimates adjusted for group and relevant covariates. Mean change ($\pm$ standard error of the mean) in five components of the Key Auditory Verbal Learning Test (RAVLT) from baseline to post-intervention in patients with mild to moderate Alzheimer's Disease. Each dot represents an individual patient. The Treatment group received therapeutic plasma exchange (TPE), and outcomes were compared to the historical control group. Arrows indicate the direction of clinical interpretation related to the test. Both, an upward arrow ($\uparrow$) and downward arrow ($\downarrow$) reflect less cognitive decline. Compared to the control group, the TPE-treated group exhibited significantly less decline across all RAVLT components: 88% less decline in RAVLT Immediate Free Recall (List A) $\uparrow$, 74% less decline in RAVLT Delayed Recall (20 min) $\uparrow$, 69% less decline in RAVLT Recognition Memory $\uparrow$, 74% fewer Intrusions $\downarrow$, 59.5% less decline in RAVLT Forgetting Percentage $\downarrow$.

45%

reduction in cognitive decline
(2.2-point MMSE difference)

88%

less decline in RAVLT
immediate recall ($p \ll 0.001$)

- Every function improved more or declined less with TPE
- TPE lowers tau and amyloid in blood and CSF: a peripheral sink, with benefit growing as abnormal proteins leave cells
- No ARIA evident with TPE

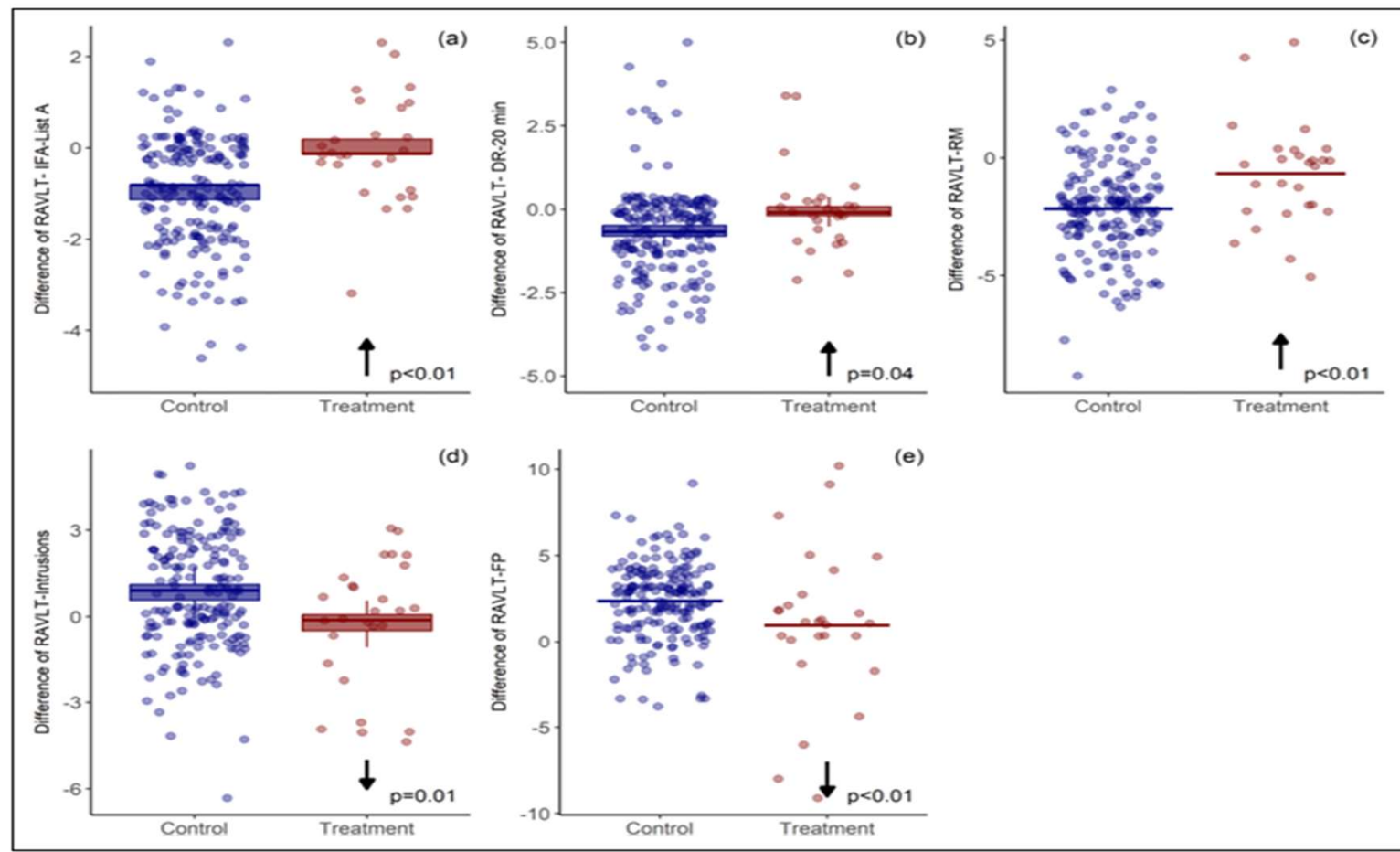


Figure 3. Memory test outcomes. Model-derived estimates adjusted for group and relevant covariates. Mean change ($\pm$ standard error of the mean) in five components of the Rey Auditory Verbal Learning Test (RAVLT) from baseline to post-intervention in patients with mild to moderate Alzheimer's Disease. Each dot represents an individual patient. The Treatment group received therapeutic plasma exchange (TPE), and outcomes were compared to the historical control group. Arrows indicate the direction of clinical interpretation related to the test. Both, an upward arrow ($\uparrow$) and downward arrow ($\downarrow$) reflect less cognitive decline. Compared to the control group, the TPE-treated group exhibited significantly less decline across all RAVLT components: 88% less decline in RAVLT

2.2 point reduction in MMSE= 45% reduction in cognitive decline

Every function improved more or declined less with TPE

TPE decreases tau and amyloid in blood and in CSF indicating a peripheral sink and benefit increasing over time as abnormal proteins come out of interstitial spaces and cells and into blood

No ARIA evident with TPE

Priority Research Paper

Rejuvenation of three germ layers tissues by exchanging old blood plasma with saline-albumin

Melod Mehdipour¹, Colin Skinner^{1,*}, Nathan Wong^{1,*}, Michael Lieb^{1,*}, Chao Liu¹, Jessy Etienne¹, Cameron Kato¹, Dobri Kiprova², Michael J. Conboy¹, Irina M. Conboy¹

¹Department of Bioengineering and QB3, UC Berkeley, Berkeley, CA 94720, USA

²California

*Equal co

Correspon

Keywords:

Received: 1

Copyright:

License (CC)

author and

ABSTRACT

Heteroch

plasma, it

young blo

blood exch

process),

“neutral”

age blood

exchange,

NBE) thus

diluting

the plasma

factors

and replen

EVERY Tissue on Microscopic Examination Appeared as if (in human terms) 40 + Years Younger-- Brain, Liver, Heart, Muscles, Immune System, Lungs, Skin.

young that animal it a be diminished if only saline was used. Our data demonstrate that a single NBE suffices to meet or exceed the rejuvenative effects of enhancing muscle repair, reducing liver adiposity and fibrosis, and increasing

Multi-Omics: TPE Drives Biological Age Rejuvenation

medRxiv preprint doi: <https://doi.org/10.1101/2024.08.02.24310303>; this version posted August 8, 2024. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. All rights reserved. No reuse allowed without permission.

Multi-omics Analysis Reveals Biomarkers that Contribute to Biological Age Rejuvenation in Response to Therapeutic Plasma Exchange

Matias Fuentealba^{1*}, Dobri Kiproff^{1,2,3}, Kevin Schnitzler¹

Jordan B. Burton¹, Mark Watson¹, Heather Halawel¹

Birgit Schilling¹, Eric Verdin^{1,3}, David Furman^{1,3}

¹ Buck Institute for Research on Aging, Novato, CA 94941

² Global Apheresis, Inc., Mill Valley, CA 94941

³ Circulate, 1424 11th Ave STE 400, Seattle, WA 98101

* These authors contributed equally to this work

Corresponding authors:

David Furman, PhD

Associate Professor and Director | Buck AI Platform,

Email: dfurman@buckinstitute.org

Eric Verdin, MD

Professor | Buck Institute for Research on Aging

Email: EVerdin@buckinstitute.org

medRxiv preprint doi: <https://doi.org/10.1101/2024.08.02.24310303>; this version posted August 8, 2024. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. All rights reserved. No reuse allowed without permission.

Results

TPE induces biological age rejuvenation and IVIG supplementation enhances the effect

Subjects underwent therapeutic plasma exchange in two temporal regimes. Ten individuals were subjected to two sessions during the first week, followed by three weeks with no sessions for 3 months (biweekly regime), and ten individuals received one session per month 6 times (monthly regime) (Figure 1A). Blood samples were taken in both regimes before sessions 1 (baseline), 4 and 6. In addition to TPE, we evaluated in ten individuals the effects of biweekly intravenous injections of immunoglobulin (IVIG) supplementation, which has previously been shown to enhance the immune system's ability to fight infections^{31,32}. The control group received sham plasma exchange, which mimicked TPE but without fluid replacement (see Methods).

Fuentealba et al., Buck Institute for Research on Aging (medRxiv preprint, 2024)

Excess DCM risk in AFR accounted for by clinical and genetic factors

AFR (compared to EUR) ancestry



1.8-fold hazards of DCM



Incident DCM cases

■ AFR = 273

■ EUR = 576

(Mean follow-up – 4.2 years)

<u>Risk factor(s)</u>	<u>% excess risk accounted for</u>
Hypertension	16%
Diabetes mellitus	9%
Chronic kidney disease	9%
rs3211938	21%
Hypertension, Diabetes mellitus, and Chronic kidney disease	25%
Hypertension, Diabetes mellitus, and Chronic kidney disease, and rs3211938	44%

~1/5 of the excess risk for DCM
among AFR individuals is
accounted for by
CD36 loss of function (rs3211938)

Table 1: AD Treatment Pipeline: Efficacy results of mAbs anti-Aβ and AMBAR

Effect size comparison across outcomes - % effect size is largest for AMBAR

		N	ADCS-ADL Effect Size	ADAS-Cog Effect Size	CDR-Sb Effect Size	ARIAs
Alzheimer's treatment candidates						
mAb anti-Aβ	Aducumumab ENGAGE	1647	18%	11%	2%	40%
	Aducumumab EMERGE (10mg/kg)	1638	40%	27%	22%	
	Lecanemab (BAN2401)	1795	37%	26%	27%	12%
MULTI-MoA	AMBAR	347	52%	66%	71%	0%

Efficacy comparative Table elaborated by the authors



25-49% Effec.



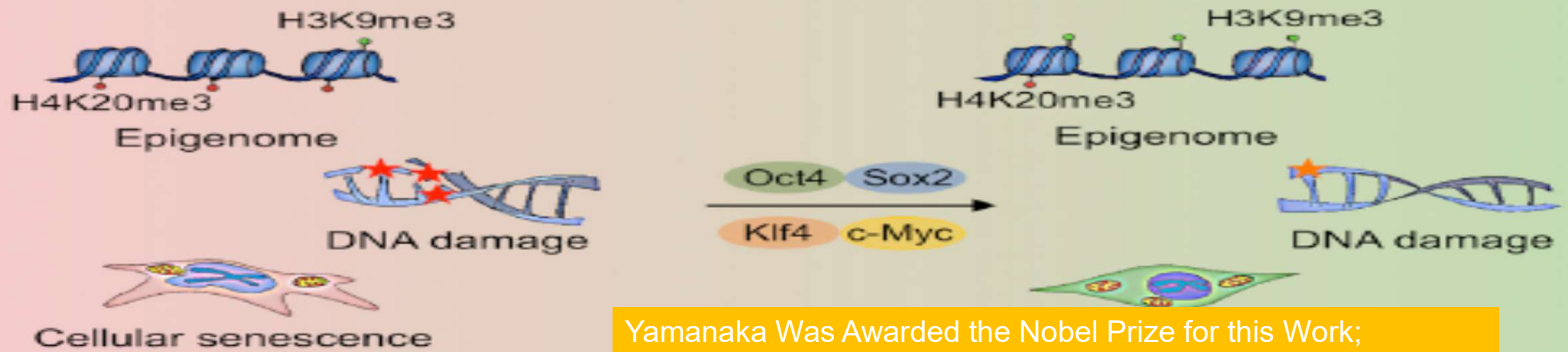
50-80% Effec.

ADCS-ADL: Alzheimer's Disease Cooperative Study-Activities of Daily Living; ADAS-Cog: Alzheimer's Disease Assessment Scale Cognitive subscale; CDR-Sb: Clinical Dementia Rating-Sum of boxes

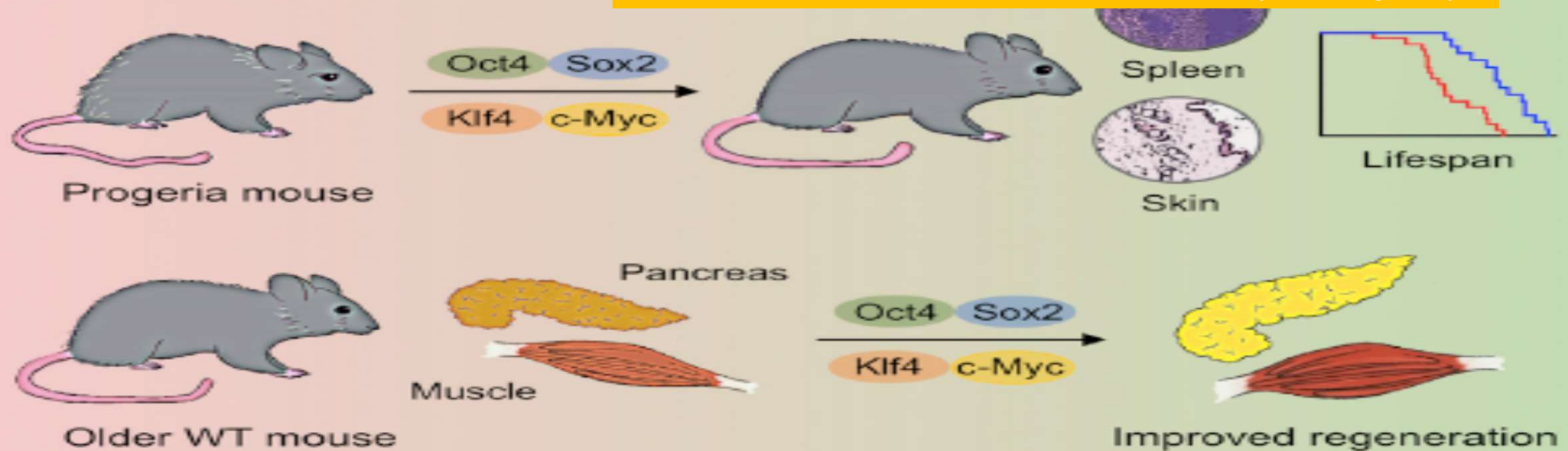
Longevity: More With An Exponential Kick: A Great Age Reboot is Likely

14 Hot Areas of Exponentially Increasing Research, Some Are:

- Senolytics --The Harvesting of Old Cells That Make Neighbors Old
- Autophagy from 5 Day Calorie/Sugar/ Protein Restriction
- Gene Editing with Immunomodulation
- Immunologic Targeting
- Stem Cells & Telomere Regeneration
- Proteostasis & Protein Inhibition
- Mitochondrial Regeneration & Elimination of Obesity with Brown Fat From White Fat
- Microbiome Reprogramming & Photomodulation
- Bionic Bodies
- Induced Tissue Regeneration and **Epigenetic Reprogramming**



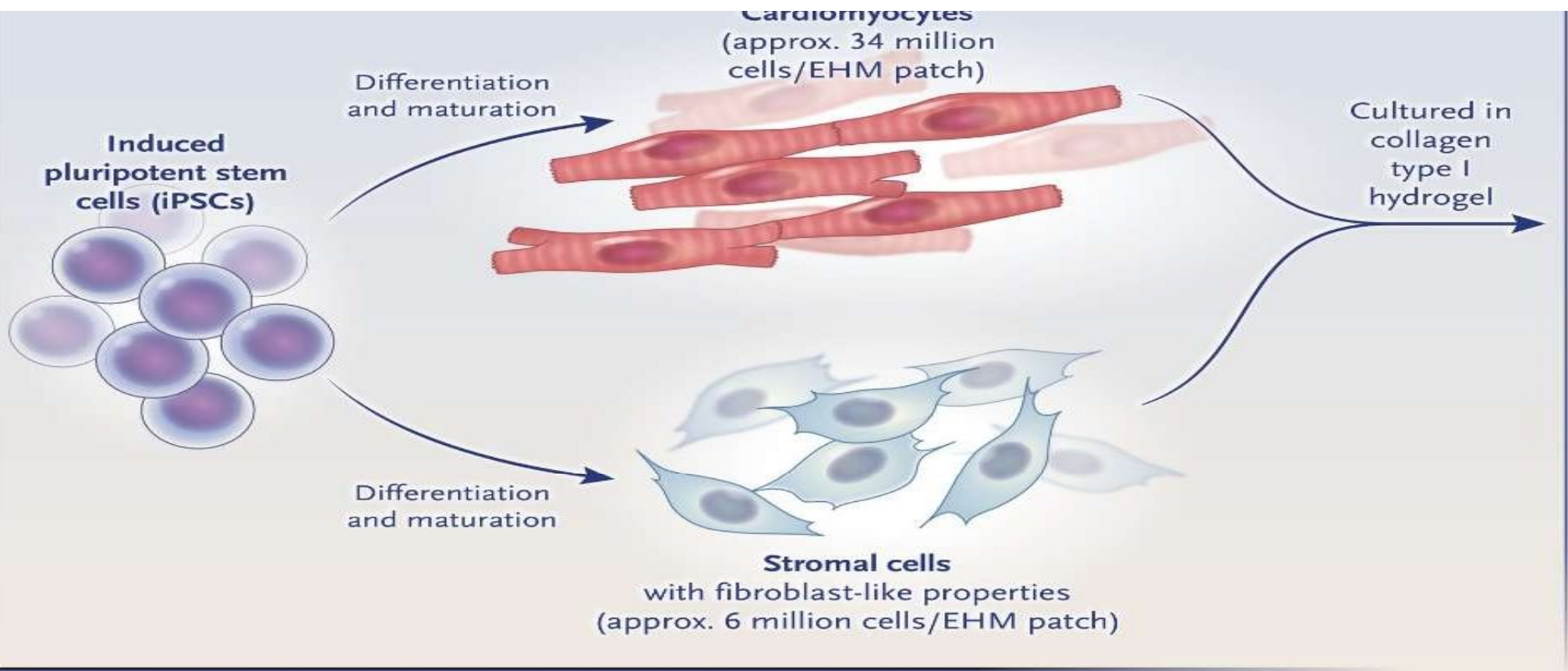
Yamanaka Was Awarded the Nobel Prize for this Work;
Now 6 Labs Including Google's Moonshot Have Replicated in 2
animal species without the increase in cancer by omitting c-Myc



Longevity: More With An Exponential Kick: A Great Age Reboot is Likely

14 Hot Areas of Exponentially Increasing Research, Some Are:

- Senolytics --The Harvesting of Old Cells That Make Neighbors Old
- Autophagy from 5 Day Calorie/Sugar/ Protein Restriction
- **Gene Editing with Immunomodulation**
- Immunologic Targeting
- **Stem Cells & Telomere Regeneration**
- Proteostasis & Protein Inhibition
- Mitochondrial Regeneration & Elimination of Obesity with Brown Fat From White Fat
- Microbiome Reprogramming & Photomodulation
- Bionic Bodies
- Induced Tissue Regeneration and Epigenetic Reprogramming



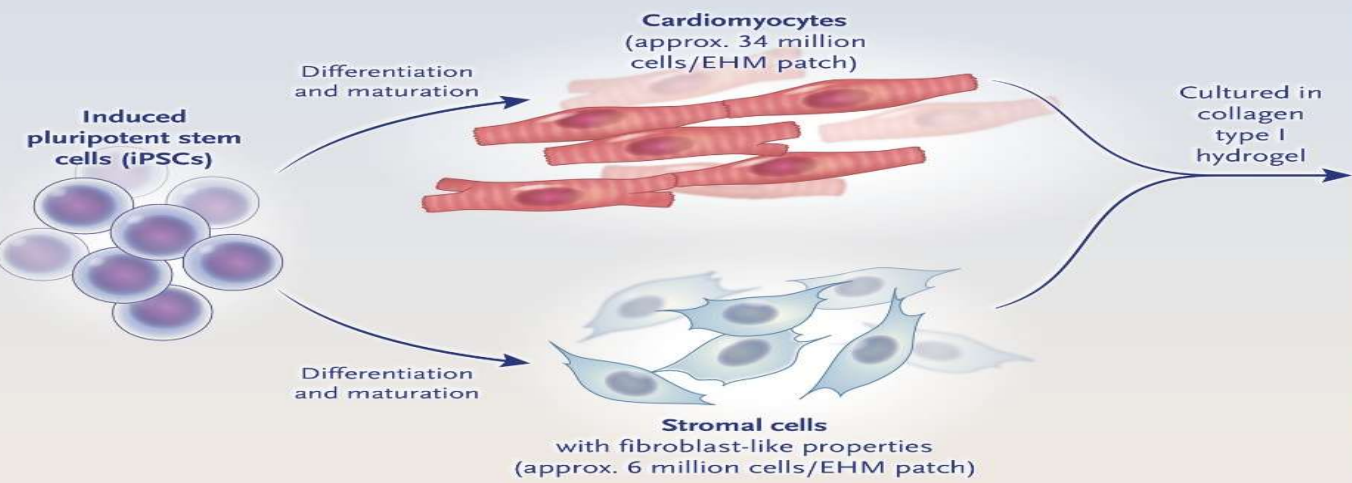
Side
view

To
view

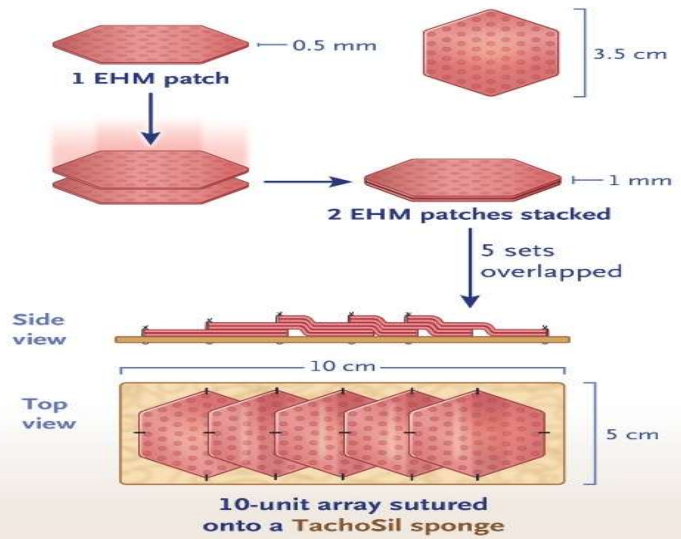
C Surgical Placement of BioVAT over Area of Cardiomyocyte Loss



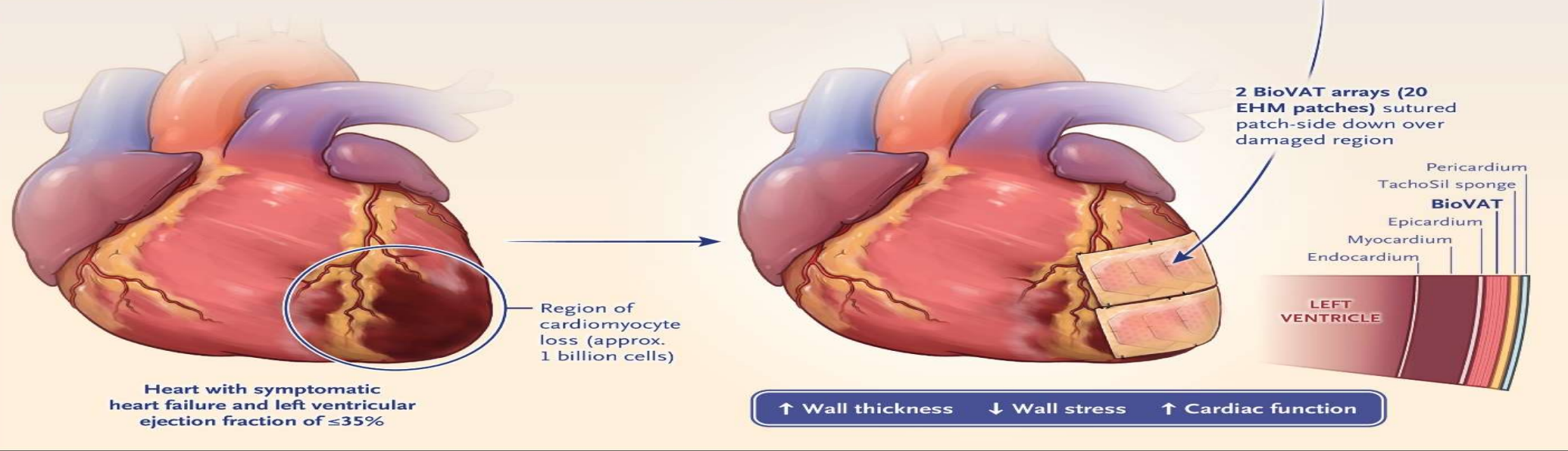
A Engineered Heart Muscle (EHM) Production



B Biologic Ventricular Assist Tissue (BioVAT)



C Surgical Placement of BioVAT over Area of Cardiomyocyte Loss



Gene Editing: Then and Now

Old (2011)		New (2025)
CRISPR-Cas9	➡	CRISPR-Cas9
Ex vivo	➡	In vivo
Blood cells	➡	Any cell
In vivo virus: some deaths	➡	In vivo lipid: fewer side effects
Scissor editing	➡	Prime editing
~\$1.2 million per treated person	➡	~\$20K per treated person

Stem Cells: Then and Now



Parkinson's disease: 3 patients (August 2025); 12 patients (July 2026)

Some Hacks to Stay Young to Get Younger in addition to TPE & GLP-1/GIP:

- Brain Functioning—Reduce unnecessary inflammation--Flu Shot
- Avoid the 5 food felons
- Ten K steps/step equivalents a day
- Speed of Processing games
- Call a Posse—Get a Coach
- Get to 6 + 2
- Inspiratory Resistance Training
- Yes on some supplements like vit D, multi, creatine, and collagen
- Stay alert to longevity choices as they become available and documented in humans

Preventing Brain Dysfunction:

- 1-8. Get to “6 Normals +2” ®: BP;ApoB/LDL; FBS/HgBA1C; Waist/Height; Cotenine; Stress
9. Manage Stress—friends & purpose
- 10-13. Do four components of physical activity
14. Do “speed of processing” games, like Double Decision and Freeze Frame
- 15,16. Eat salmon or ocean trout or 900mg DHA and ½ Tbspoon of EVOO daily
- 17,18. Eat only when the sun is up and do 5 days a month of Fasting Mimicking Diet
19. Avoid *sssssnake oil foods*
- 20-21. Give sleep respect and take your vacations
22. Avoid toxins (tobacco, vapes, BPA, texting, wallet-biopsy supplements)
23. Drink coffee if you’re a *fast metabolizer*—no additives
24. Enjoy nuts
25. Enjoy blueberries
26. Take the Fab 15+--supplements and small molecules including a Multi, Vit D3/K2, Phospho-creatine, Bumetamide and 11+ others
27. Stay up to date on Rx’s for aging
28. Do preventive procedures
29. Enjoy an infrared sauna for 20 minutes, four times each week
- 30-31. Decrease inflammation. Floss and see dental pro
32. **Keep immunizations up to date**
- 33-35. Smell the roses (olfactory) and keep hearing (music stimulation) and eyesight
- 36-40. Enjoy Leafy greens, lycopene, and consider HT with ASA and Bovine Colostrum

Hacks to Stay Young to Get Younger

In addition to TPE and GLP-1/GIP

1

Get a flu shot

Reduce unnecessary brain inflammation

2

Avoid the 5 food felons

3

10,000 steps a day

Or step equivalents

4

Speed-of-processing games

5

Call a posse

Get a coach

6

Get to 6 + 2

The 6 Normals + 2

7

Inspiratory resistance training

8

Yes to some supplements

Vitamin D, a multi, creatine and collagen

9

Stay alert

Adopt longevity choices as they are documented in humans

Preventing Brain Dysfunction: Choices 1–19

1–8

Get to the “6 Normals + 2”®: BP; ApoB/LDL; FBS/HbA1c; waist/height; cotinine; stress

9

Manage stress: friends and purpose

10–13

Do the four components of physical activity

14

Do speed-of-processing games, like Double Decision and Freeze Frame

15–16

Eat salmon or ocean trout (or 900 mg DHA) and ½ tablespoon of EVOO daily

17–18

Eat only when the sun is up, and do 5 days a month of a fasting-mimicking diet

19

Avoid snake-oil foods

Preventing Brain Dysfunction: Choices 20–40

20–21 Give sleep respect, and take your vacations

22 Avoid toxins: tobacco, vapes, BPA, texting, wallet-biopsy supplements

23 Drink coffee if you're a fast metabolizer, with no additives

24 Enjoy nuts

25 Enjoy blueberries

26 Take the Fab 15+ supplements and small molecules, including a multi, vitamin D3/K2, phosphocreatine, bumetanide and 11+ others

27 Stay up to date on Rx's for aging

28 Do preventive procedures

29 Enjoy an infrared sauna for 20 minutes, four times a week

30–31 Decrease inflammation: floss and see a dental pro

32 Keep immunizations up to date

33–35 Smell the roses (olfactory), and keep your hearing (music stimulation) and eyesight

36–40 Enjoy leafy greens and lycopene, and consider HT with ASA and bovine colostrum

Preserve Your Brain: Decrease Inflammation

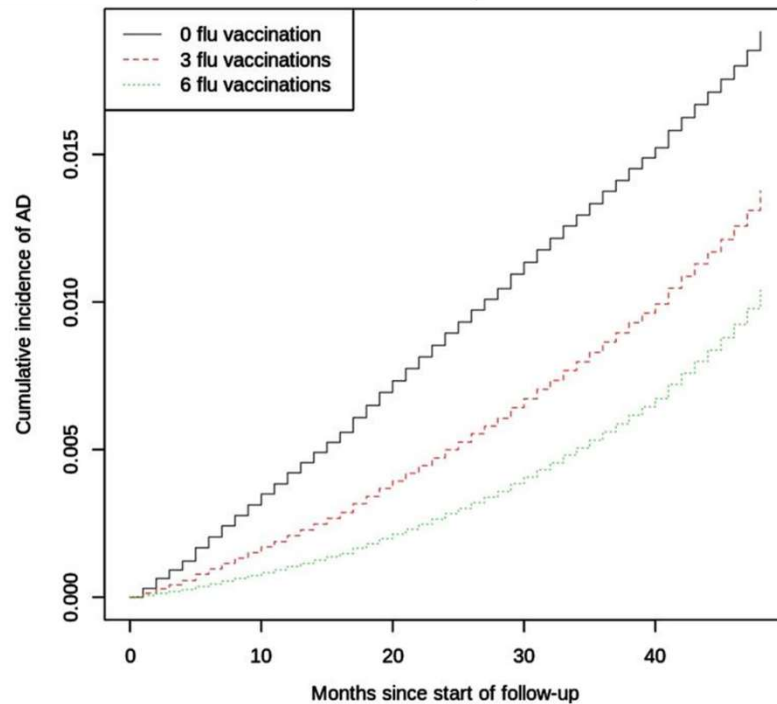


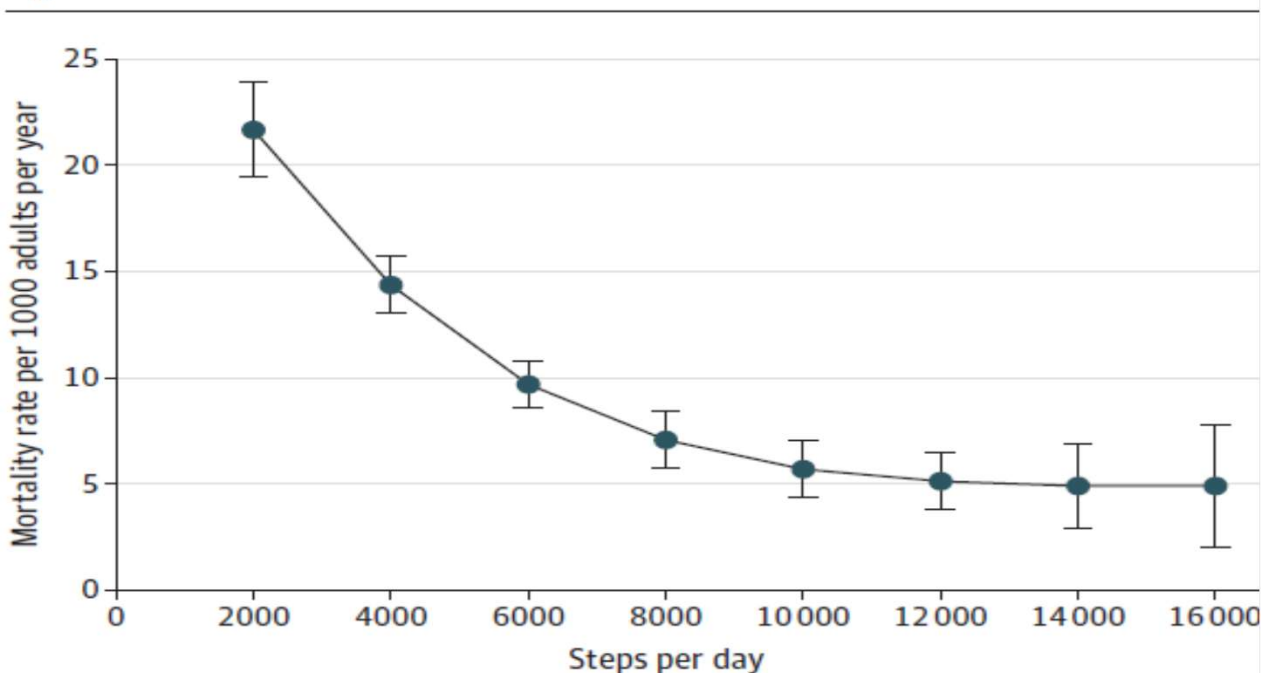
Figure: Estimated cumulative incidence function of AD incidence by number of influenza vaccinations. Source: [Bukhbinder et al.](#)

40%

reduction in dementia with 6
years of influenza vaccination

*Cumulative incidence of AD by number of influenza
vaccinations (0, 3, 6)*

Figure 1. Steps per Day and All-Cause Mortality in a Study of the Association of Daily Step Count and Step Intensity With Mortality Among US Adults Aged at Least 40 Years



Mortality rates were adjusted for age; diet quality; sex; race/ethnicity; body mass index; education; alcohol consumption; smoking status; diagnoses of diabetes, stroke, coronary heart disease, heart failure, cancer, chronic bronchitis, and emphysema; mobility limitation; and self-reported general health. Rates were computed using the 2003 mortality rate for US adults (11.4 deaths per 1000 adults per year). Models included US population and study design weights to account for the complex survey design and models were replicated 5 times to account for imputed steps data. Error bars indicate 95% CIs.

JAMA. 2020;323(12):1151-1160. doi:10.1001/jama.2020.1382

Figure 2. Steps per Day and Mortality by Sex, Age, and Race/Ethnicity in a Study of the Association of Step Count and Intensity With Mortality

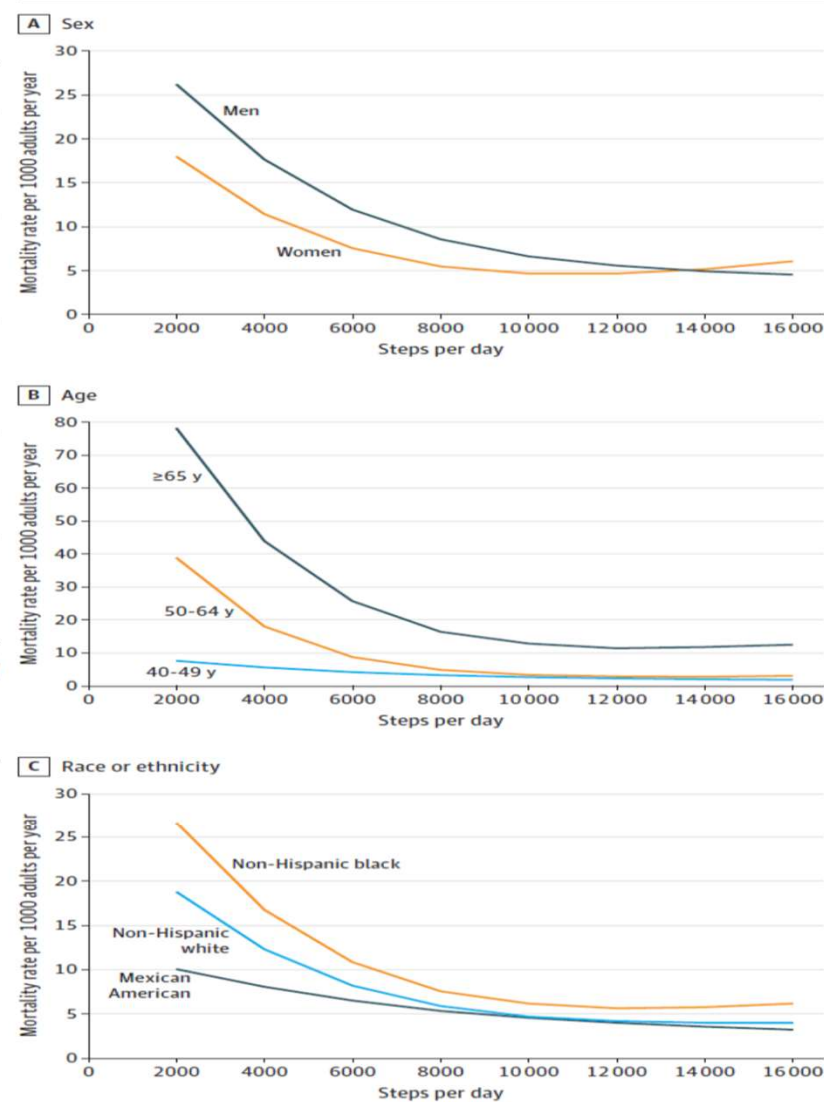
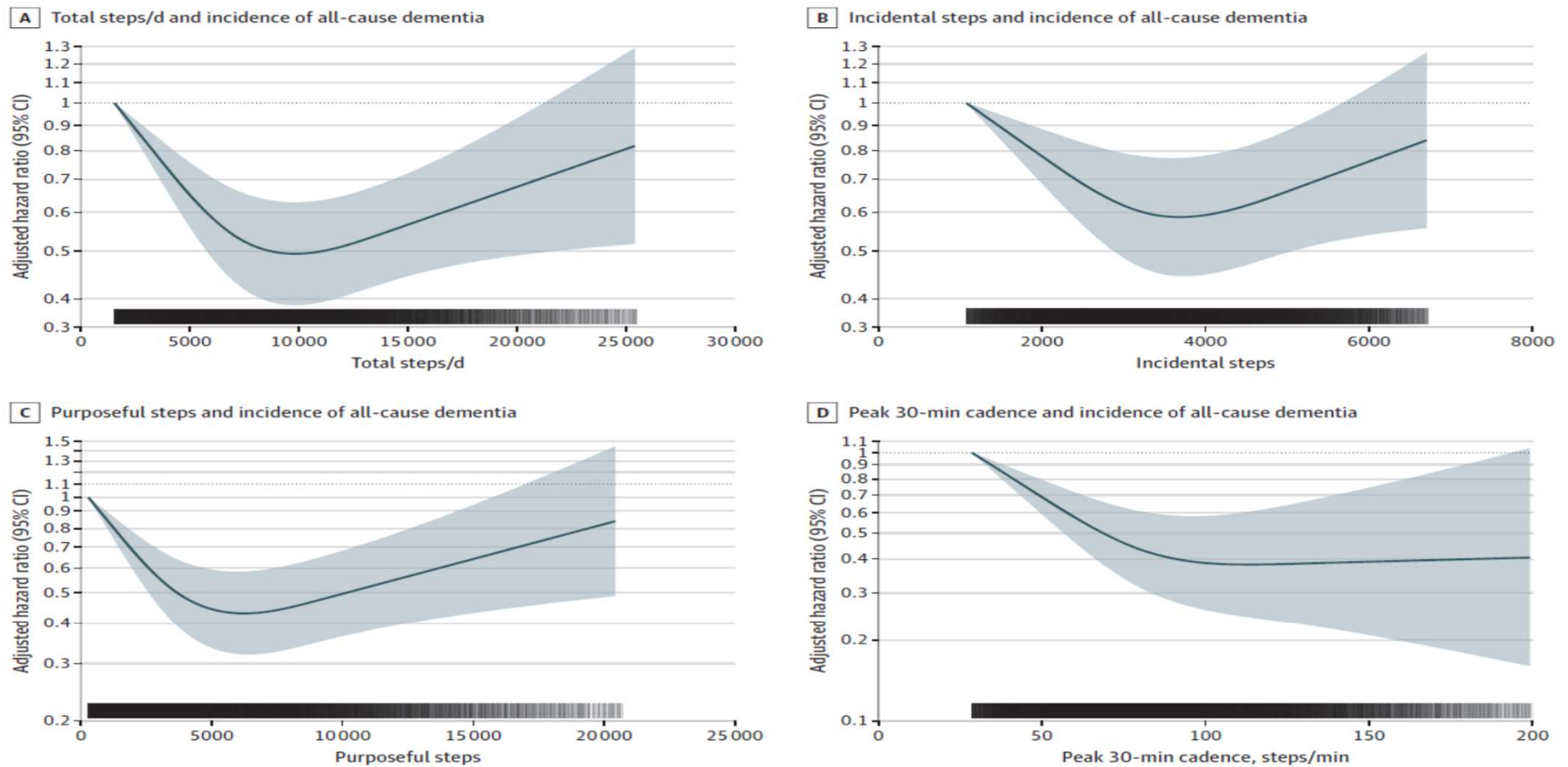


Figure 2. Dose-Response Association Between Different Accelerometer-Measured Step-Based Metrics and Incidence of All-Cause Dementia



Shading indicates 95% CIs; solid lines, hazard ratios, in logarithmic scale, adjusted for age, sex, race, education, Townsend deprivation index, smoking, alcohol use, fruit and vegetable consumption, family history of cardiovascular disease and cancer, medication use (cholesterol, insulin, and hypertension), accelerometer-measured sleep, and days wearing accelerometer. For incidental steps, models were further adjusted for purposeful steps (and vice versa). For peak 30-minute steps, models were additionally adjusted for total steps per

day. Total steps per day indicates the mean number of steps accumulated in a day; incidental steps, the total daily steps at 1-39 steps per minute; purposeful steps, the total daily steps at ≥ 40 steps per minute; peak 30-minute cadence, the mean steps per minute recorded for the 30 highest, not necessarily consecutive, minutes in a day. Dose-response associations were assessed with restricted cubic splines with knots at 10th, 50th, and 90th centiles of the distribution of the exposure of interest.

Speed of Processing Games

- Advanced Cognitive Training in Vital Elderly study: a RCT (N = 2802) among initially healthy older adults, to examine 3 cognitive training programs (memory, reasoning, or speed of processing) relative to a no-contact control condition
- Speed training resulted in reduced risk of dementia (hazard ratio [HR] 0.71, [CI] 0.50–0.998, $P = .049$)
- Memory and reasoning training did not (HR 0.79, 95% CI 0.57–1.11, $P = .177$ and HR 0.79, 95% CI 0.56–1.10, $P = .163$, respectively).
- Each additional 2 hr speed training session was associated with a 10% lower hazard for dementia (unadjusted HR, 0.90; 95% CI, 0.85–0.95, $P < .001$).

Healthy older adults doing 10 hrs S of P training had a 29% reduction in dementia after 10 years of follow-up compared to the untreated control group. Those doing 18 hrs has a 48% reduction in dementia.

Speed-of-Processing Games Reduce Dementia Risk

ACTIVE trial (Advanced Cognitive Training for Independent and Vital Elderly): RCT, N = 2,802 healthy older adults

29%

lower dementia risk with speed training after 10 years (HR 0.71; 95% CI 0.50–0.998; P = .049)

48%

reduction in dementia for those completing 18 hours of speed training

10%

lower dementia hazard for each additional 2-hour session (HR 0.90; 95% CI 0.85–0.95; P < .001)

Memory and reasoning training did not reduce risk (HR 0.79, P = .177 and HR 0.79, P = .163)

Source: <https://doi.org/10.1016/j.trci.2017.09.002>



Want to try out our new training selection features?

30

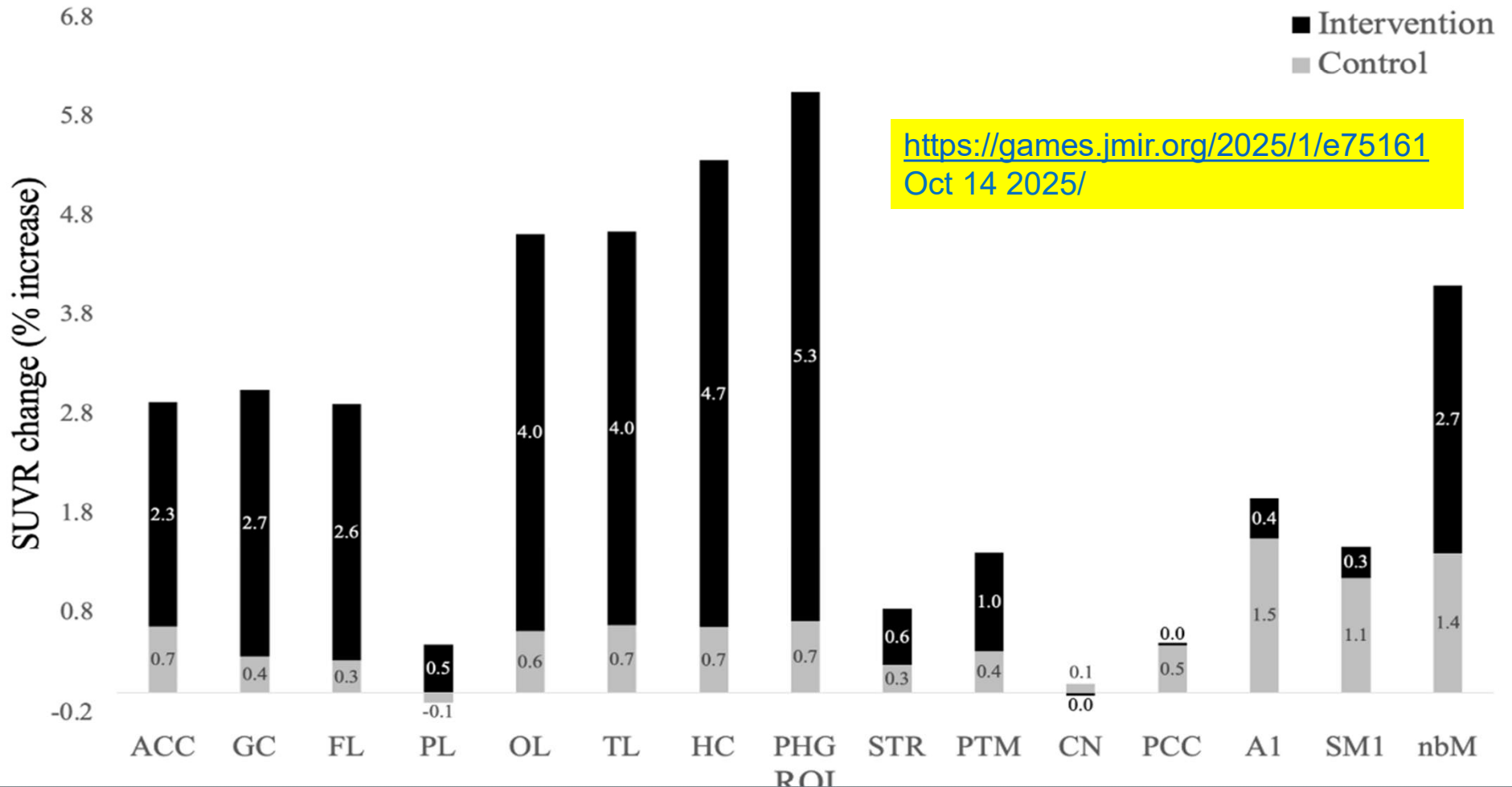


500 ms

See objects fast



Figure 4. Standard uptake value ratio (SUVR) binding percent increases. Percent change in SUVR binding from baseline to posttest across regions of interest (ROIs) for the intervention and active control groups. Higher scores indicate greater increases in binding. A1: primary auditory cortex; ACC: anterior cingulate cortex; CN: caudate; FL: frontal lobe; GC: global cortex; HC: hippocampus; nbM: nucleus basalis of Meynert; OL: occipital lobe; PCC: posterior cingulate cortex; PHG: parahippocampal gyrus; PL: parietal lobe; PTM: putamen; SMI: primary sensorimotor cortex; STR: striatum; TL: temporal lobe.

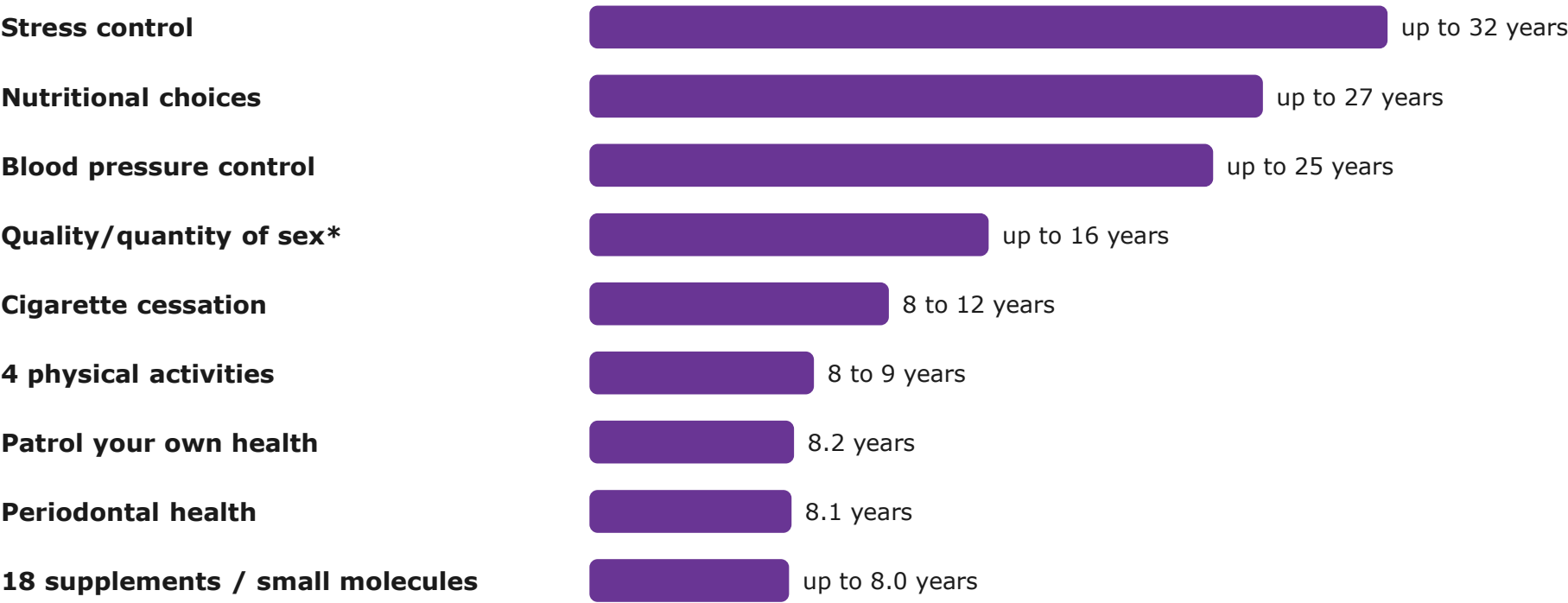


Make Your *RealAge* Younger

	Years Younger
✓ BP Control	up to 25 years
✓ Cigarette Cessation	8- 12 years
✓ Stress Control	up to 32 years
✓ Patrol Own Health	8.2 years
✓ Quality/Quantity of Sex	up to 16 yrs
✓ Nutritional Choices	up to 27 years

Make Your *RealAge* Younger: The Full Picture

Years younger in risk of disability and death at age 58, versus the average of all other choices



**Mutually monogamous; excludes STD risk.*

5 Tips to Prepare Personally for the Reboot

1 **Change your attitude**

You are a genetic engineer for **YOU**.

2 **Eat what you love**

Only eat food you love that loves your body back.

3 **Choose your team**

For trust, honesty, knowledge and curiosity, to assess your body and brain.

4 **Add speed**

To your body and brain; plus smells, coffee and olive oil daily.

5 **Manage stress**

Including cultivating your posse and purpose.

Some Views on Specific Supplements and Small Molecules:

1. Vit D2/3 + K2
2. Multi
3. DHA/EPA-Omega-3
4. Ca⁺⁺/Mg⁺⁺
5. Statin
6. GLP-1-GIP-? Other Peptides, & probably SGLT2's
7. ASU
8. CoQ10
9. Collagen/Gelatin/
10. Creatine
11. Tumeric with piperine
12. Baby Aspirin 2x as day
13. Spermadine
14. Specific Probiotics
15. Bovine Colostum
16. Fiber/ SCFA
17. Colchicine
18. PDE5-i

Some not to bother with—wallet biopsies as of now—either not enough data or just continually fail human tests:

Of 55, 37 –the majority fit this category—some of the major ones:

NAD: great animal data; fails all but specific mitochondrial deficit diseases human tests so far.

Resveratrol: great animal data; fails all human tests so far.

Metformin: USA data epidemiologic look great; Netherlands data look opposite—causes aging. Do not use if exercise

ACV—no benefit

Rapalogues—promising but no positive human data so far

Urolitin A – promising but not enough human data so far

Melatonin Maybe for sleep and sepsis and jet lag but no long term ACM or disability studies

Ashwaghandha –good releasing agent; no long term ACM or disability studies