26 AUGUST — 30 AUGUST

ARDD 2024 THE 11th AGING RESEARCH & DRUG DISCOVERY MEETING

XPRIZE HEALTHSPAN

TAKING AIM AT AGING: XPRIZE HEALTHSPAN TEAM SUMMIT MAKES ITS DEBUT AT THE 11TH ARDD

UNIVERSITY OF COPENHAGEN

Insilico Medicine

Register at agingpharma.org

#XPRIZEHealthspan #ARDD2024

XPRIZE HEALTHSPAN INAUGURAL TEAM SUMMIT

Hosted at the 11th ARDD Meeting

THE PRIZE THAT PROVED OUR CONCEPT

ANSARI PRIZE

OCT 04, 2004 | $10M

GALVANIZED NEW ERA OF COMMERCIAL SPACE TRAVEL

30 YEARS | 30 PRIZES | 30X IMPACT

Oc Wendy Schmidt Oil Cleanup	**Oh** Wendy Schmidt Ocean Health	**So** Shell Ocean Discovery	**R** Rainforest	**Wf** Wildfire	**Nc** NRG Cosia Carbon	**Cr** Carbon Removal	**Ai** IBM Watson Ai	**Aa** ANA Avatar	**Qa** Quantum Applications
2010 - 2011 $1.4M	2013 - 2015 $2M	2015 - 2019 $7M	Active $10M	Active $11M	2015 - 2020 $20M	Active $100M	2016 - 2020 $5M	2018 - 2022 $10M	Active $5M
Wa Water Abundance	**Fb** Feed the Next Billion	**Ws** Water Scarcity	**Ag** Archon Genomics	**Ns** Nokia Sensing	**Qt** Qualcomm Tricorder	**Nm** Next Gen Mask	**Rt** Rapid COVID Testing	**Pr** Pandemic Response	**Hs** Healthspan
2016 - 2018 $1.75M	Active $15M	Active $119M	Canceled $10M	2012 - 2014 $2.25M	2012 - 2017 $10M	2020 $1M	2020 - 2021 $6M	2020 - 2021 $500K	Active $101M
Gle Global Learning	**Bb** Barbara Bush Fdn. Adult Literacy	**Cc** Barbara Bush Fdn. Adult Literacy Comm. Comp.	**An** Anu + Naveen Jain Women's Safety	**Rr** Rapid Reskilling	**Dl** Digital Learning	**A** Ansari	**Nl** Northrop Grumman Lunar Landing	**Gl** Google Lunar	**Pa** Progressive Automotive
2014 - 2019 $15M	2015 - 2019 $7M	2015 - 2019 $1M	2016 - 2018 $1.2M	2020 - 2023 $5M	2021 - 2023 $1M	1996 - 2004 $10M	2006 - 2009 $2M	2007 - 2018 $40M	2008 - 2010 $10M

6 HEALTH DOMAIN PRIZES

Ns
Nokia Sensing
2012 - 2014
$2.25M

Qt
Qualcomm Tricorder
2012 - 2017
$10M

Nm
Next Gen Mask
2020
$1M

Rt
Rapid COVID Testing
2020 - 2021
$6M

Pr
Pandemic Response
2020 - 2021
$500K

Hs
Healthspan
Active
$111M

XPRIZE HEALTHSPAN | HEVOLUTION | SOLVE FSHD

HEVOLUTION	CHIP WILSON / SOLVE FSHD
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NANCY & HOWARD MARKS	ELEANOR & HOWARD MORGAN FAMILY FOUNDATION
CHRIS OUWINGA	CHRISTIAN PENEFF
SENEGENCE	MARK S. SIEGEL
TODD WANEK	SERGEY YOUNG


If a therapeutic could
IMPROVE
HEALTHSPAN...
how would we know?

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Endowed Chair of Healthy Aging, UAB

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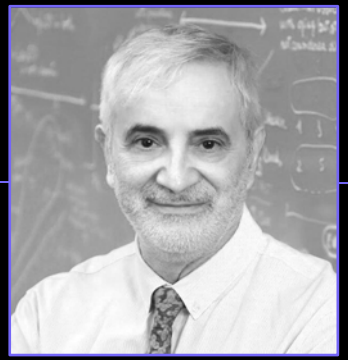
Director, UCLA Broad Stem Cell Research Center



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Scientific Director, National Institute on Aging

PETER H. DIAMANDIS, MD

MEHMOOD KHAN, PHD

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XPRIZE HEALTHSPAN | HEVOLUTION | SOLVE FSHD

01

PRIZE OVERVIEW

XPRIZE HEALTHSPAN OVERVIEW

JAMIE JUSTICE, PHD
XPRIZE Healthspan

NICHOLAS SCHORK, PHD
Translational Genomics Research Institute (TGen)

EVA CHIN, PHD
SOLVE FSHD

XPRIZE HEALTHSPAN | HEVOLUTION | SOLVE F.S.H.D

XPRIZE HEALTHSPAN

A 7-YEAR, $101M GLOBAL COMPETITION

INAUGURAL TEAM SUMMIT
HOSTED AT AGING RESEARCH & DRUG DISCOVERY (ARDD)
26 AUGUST 2024

01

XPRIZE HEALTHSPAN

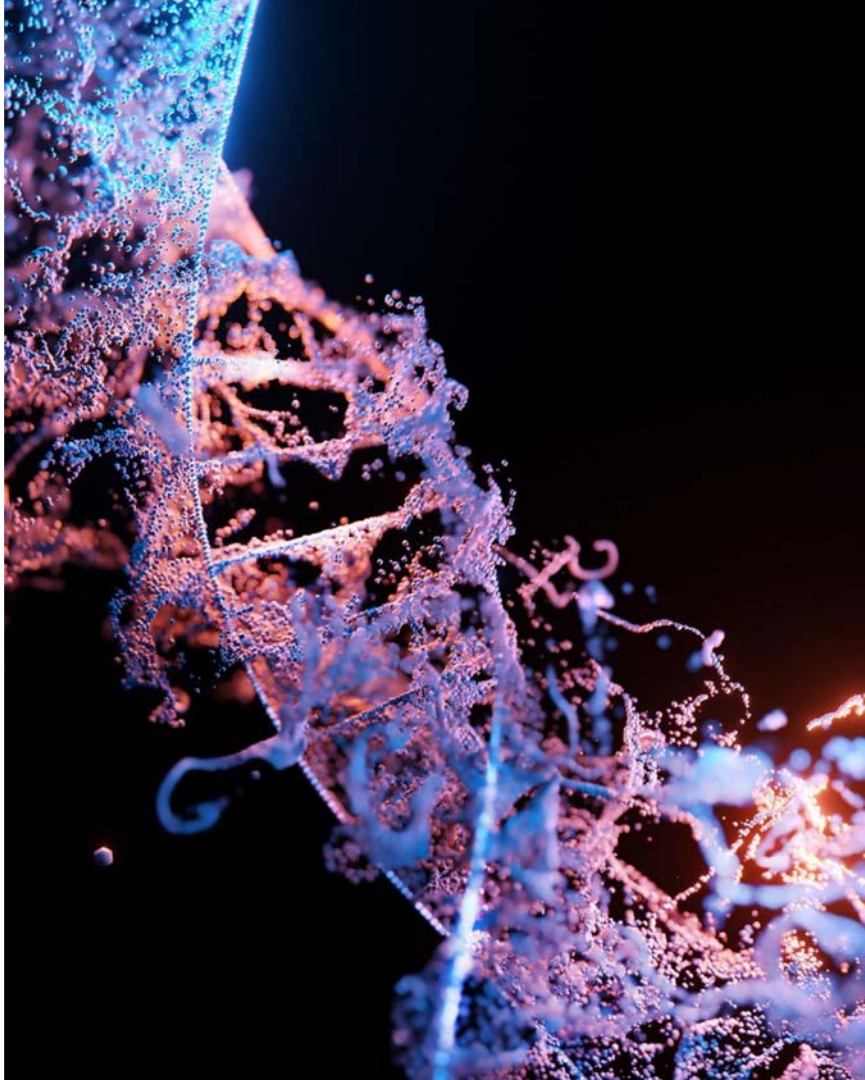
WHY AN XPRIZE ON HEALTHSPAN?

OUR GLOBAL POPULATION IS AGING

This should be cause for celebration, but innovative solutions to address age-related health declines are **URGENTLY NEEDED**

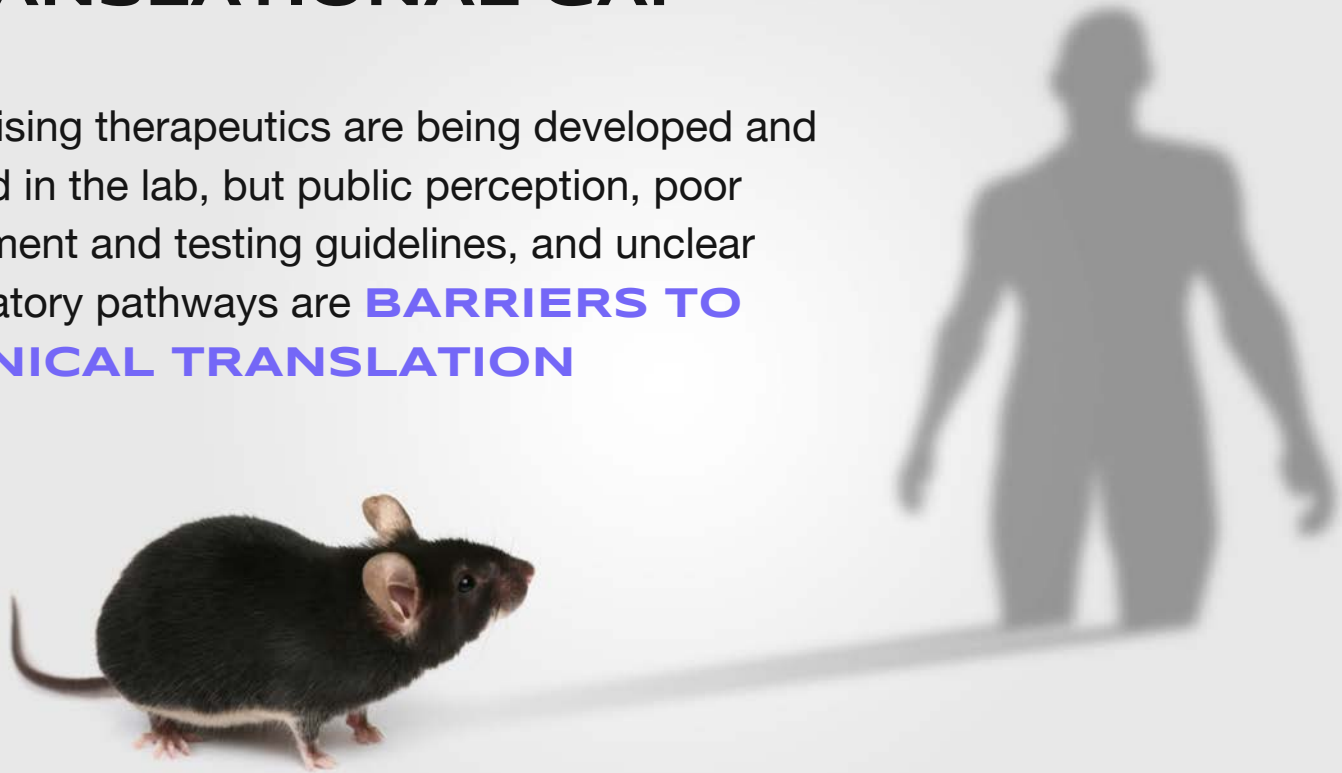
AGING HAS A DISTINCT BIOLOGY

This biology can be targeted by therapeutics to **EXTEND LIFESPAN AND HEALTHSPAN** in animal models



TRANSLATIONAL GAP

Promising therapeutics are being developed and tested in the lab, but public perception, poor alignment and testing guidelines, and unclear regulatory pathways are **BARRIERS TO CLINICAL TRANSLATION**



THE MISSION OF XPRIZE HEALTHSPAN

- Provide **proof of concept** that biological aging is a target for therapeutic development.
- Create a **global research network** in healthspan and aging research by identifying and aligning labs, companies, and researchers
- Stimulate **important investments** in longevity, biology of aging, and biotech
- **Develop methodologies** for measuring healthspan in early-stage trials
- Build public awareness and new therapeutic options for **persons aging with FSHD**

02

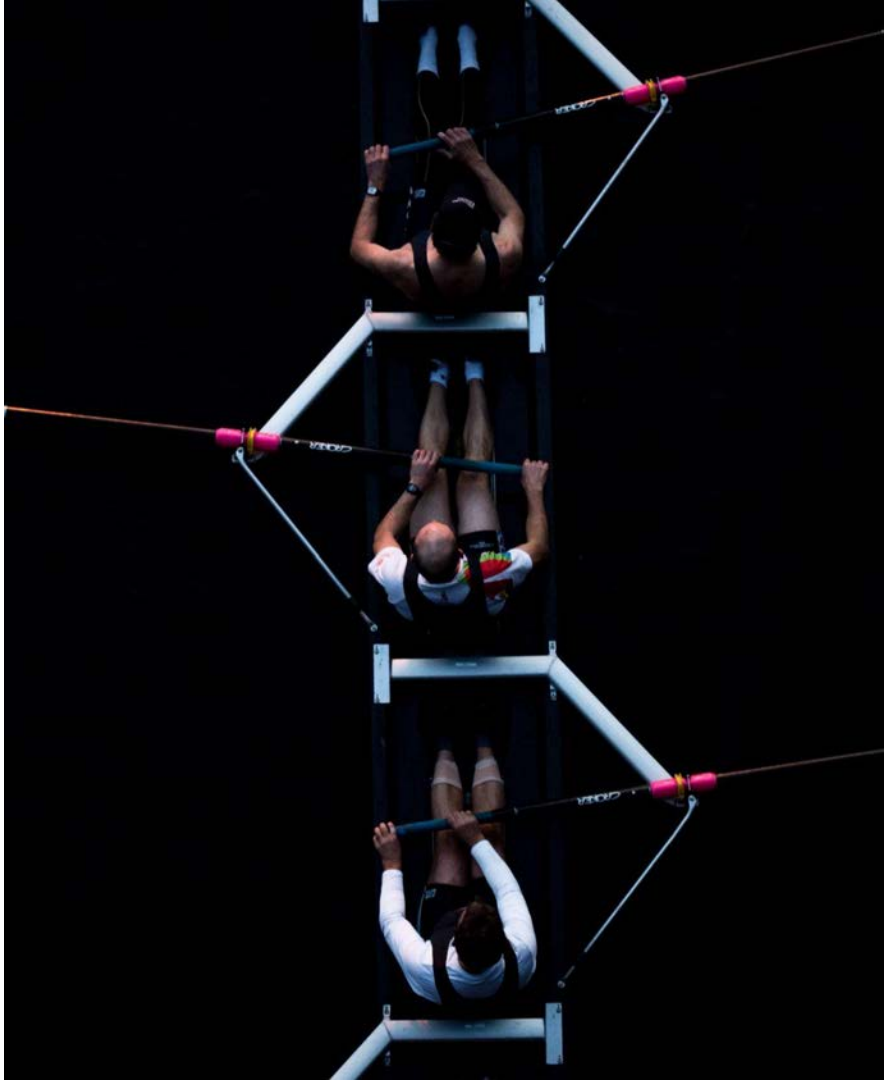
XPRIZE HEALTHSPAN
COMPETITION OVERVIEW

TESTING & JUDGING

The **WINNING TEAM** must demonstrate that their therapeutic treatment restores muscle, cognitive, and immune function in older persons. The therapeutic treatment must take 1-year or less.

Awarding of the best team will be indexed to improvements in function relative to age-related declines expected over:

- 10 years ($61M);
- 15 years ($71M);
- Or 20 years ($81M)



TESTING & JUDGING

QUALIFYING SUBMISSION

Research
& Development

Milestone 1:

- $10M
- $2M FSHD

SEMI-FINALS

Proof-of- Concept
Clinical Studies

Milestone 2:

- $10M

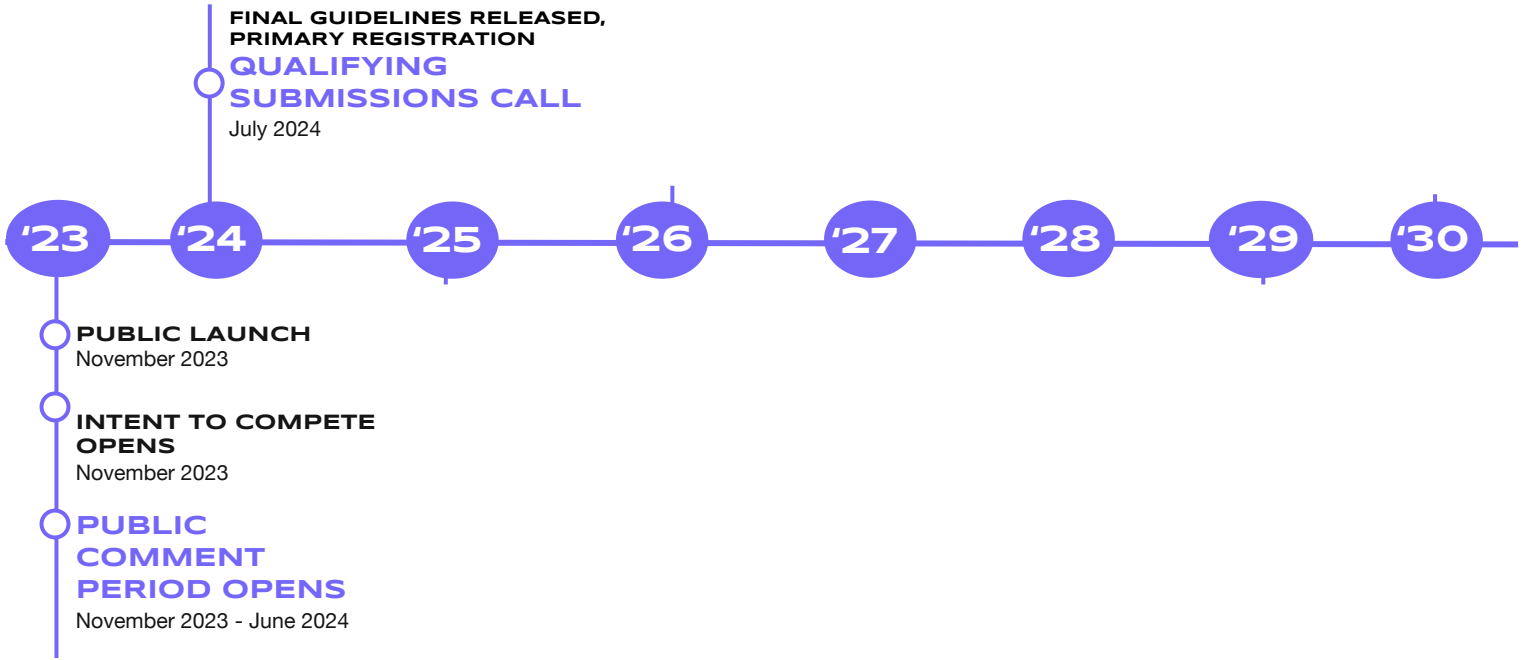
FINALS

1-year Clinical Trials in
Older Adults

Grand Prize:

- Up to $81M
- $8M FSHD

KEY MILESTONES



TEAM REGISTRATION OVERVIEW

411

TEAMS PRE-REGISTERED

53

COUNTRIES

03

XPRIZE HEALTHSPAN

HOW TO WIN: MILESTONE 1 QUALIFYING SUBMISSIONS

QUALIFYING SUBMISSION

DUE 20 DECEMBER 2024!

PURPOSE: first formal opportunity for teams to demonstrate their ability to compete in the $101M competition

QUALIFYING SUBMISSION

Research
& Development

Milestone 1:

- $10M
- $2M FSHD

Approximately 12 pages

- Summary……1pg
- Team ……2pg
- Environment and Clinical Centers……. 2pg
- Technical Application……5pg
- Study Timeline…….. 1pg
- Scalability / Accessibility…… 1pg

\+ Human Subjects Safety, Resourcing Plan, Biohazard

04

XPRIZE HEALTHSPAN

HOW TO WIN: MILESTONE 2 SEMI-FINALS

SEMI-FINALS TESTING & JUDGING

SEMI-FINALS

Proof-of- Concept Clinical Studies

Milestone 2:

- $10M

EARLY STAGE / PROOF-OF-CONCEPT CLINICAL STUDIES

Typically short (less than 30-60 days), small (5-20 people receive active intervention), and relatively inexpensive studies that are used to help design and justify larger clinical trials

For XPRIZE Healthspan Semifinals, these trials are used to indicate readiness for Finals and feasibility of approach

OUR TOP CONCERN: SAFETY

All competing teams will be required to have:

- Their studies reviewed and approved by an IRB, either institutional or central
- A data and safety monitoring plan
- A medical oversight plan
- Risk minimizing plan

Teams are required to communicate occurrence of adverse events to XPRIZE

05

XPRIZE HEALTHSPAN

HOW TO WIN: GRAND PRIZE FINALS

HOW TO WIN: HEALTHSPAN GRAND PRIZE

FINALS

1-year Clinical Trials in Older Adults

Grand Prize:

- Up to $81M
- $8M FSHD

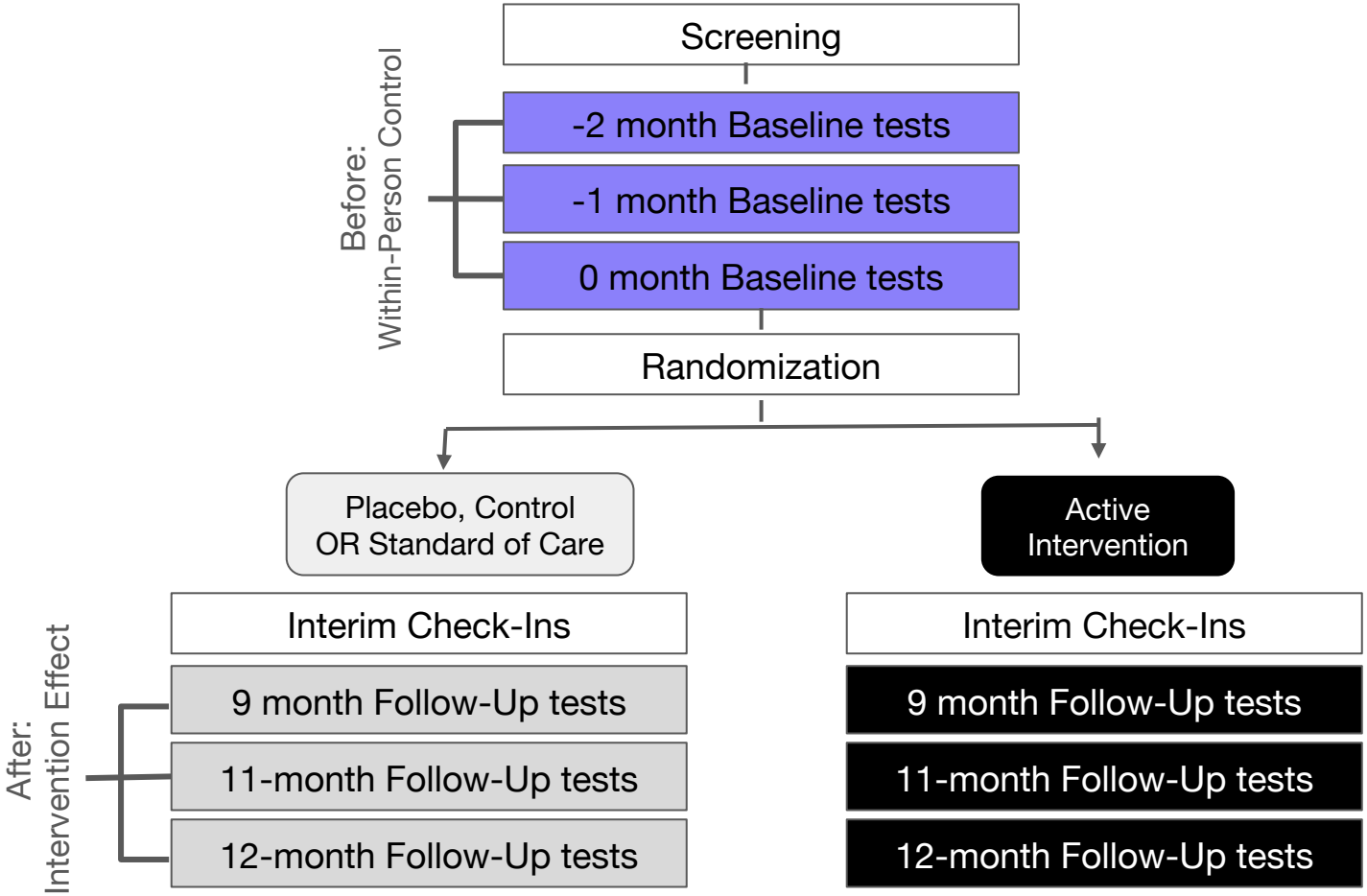
POPULATION: Persons aged 50-80 years who are free of life-threatening major disease or disability

INTERVENTION: Team discretion. Safety is priority.

CONTROL: Required, but specifics depends on intervention

OUTCOMES: Improvement in muscle, cognitive, AND immune function

TIME: Follow-up testing one year after therapeutic start


Screening
Before:
Within-Person Control
-2 month Baseline tests
-1 month Baseline tests
0 month Baseline tests
Randomization
Placebo, Control
OR Standard of Care
Active
Intervention
After:
Intervention Effect
Interim Check-Ins
9 month Follow-Up tests
11-month Follow-Up tests
12-month Follow-Up tests
Interim Check-Ins
9 month Follow-Up tests
11-month Follow-Up tests
12-month Follow-Up tests

HOW TO WIN: HEALTHSPAN GRAND PRIZE

SINGLE CROSSOVER DESIGN WITH PERSONALIZED RESPONSE THRESHOLDS

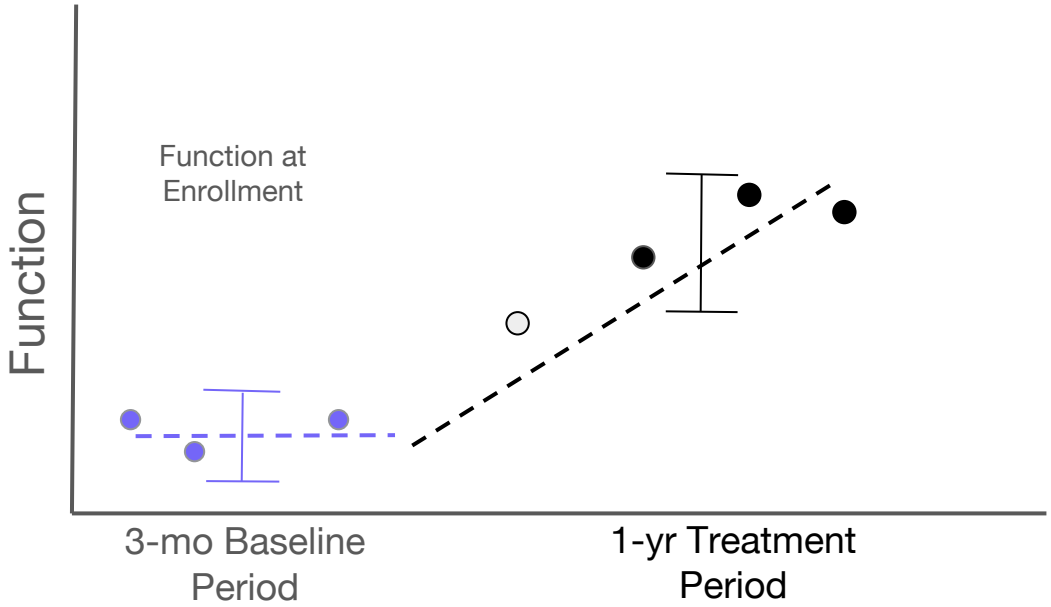


Figure courtesy Schork & Goetz

HOW TO WIN: HEALTHSPAN GRAND PRIZE

SINGLE CROSSOVER DESIGN WITH PERSONALIZED RESPONSE THRESHOLDS

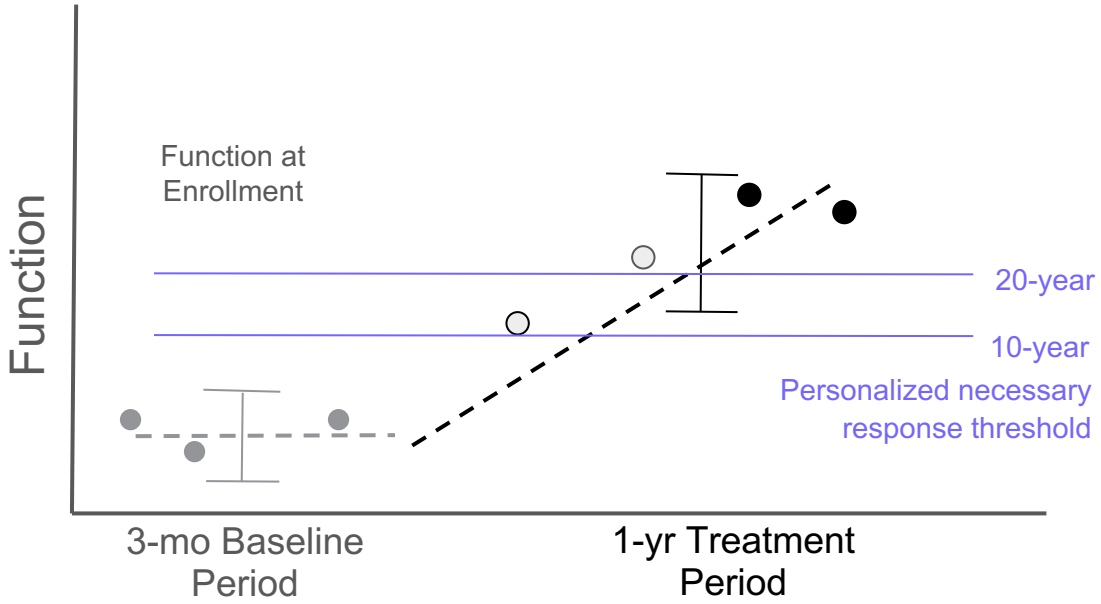
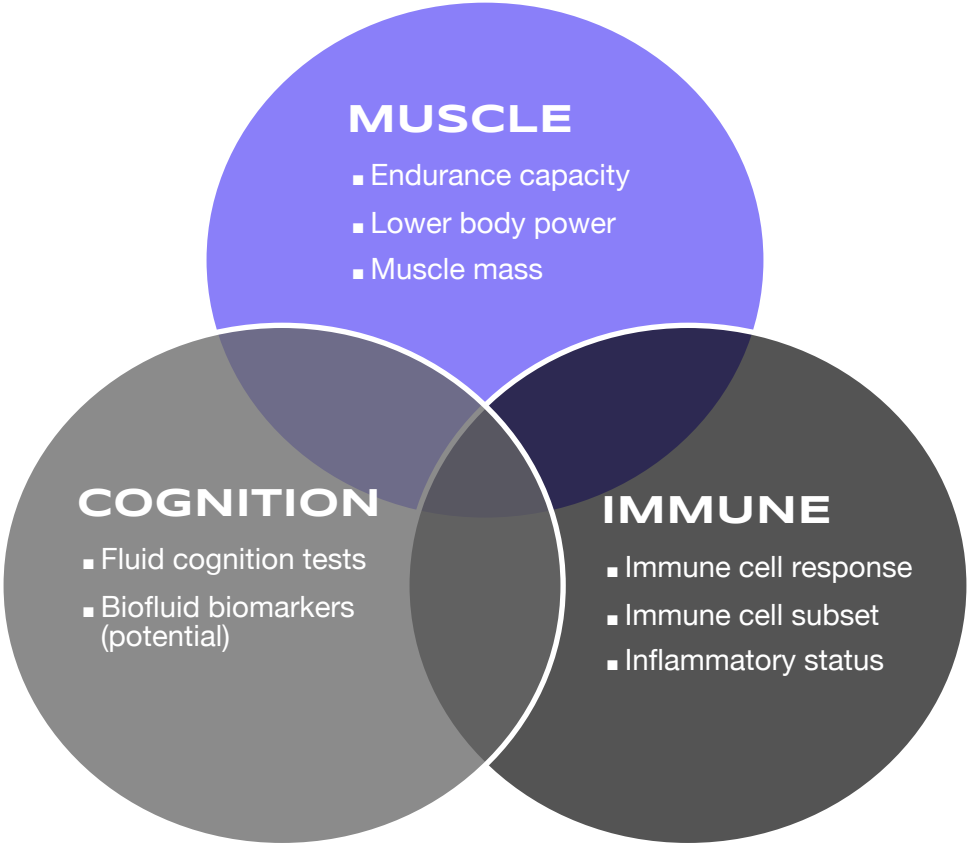


Figure courtesy Schork & Goetz

HOW TO WIN: HEALTHSPAN GRAND PRIZE



HOW TO WIN: HEALTHSPAN GRAND PRIZE

MUSCLE			
Subdomain	**Type**	**Optimal Measure**	**Acceptable Measure**
Endurance Capacity	Function	Cardiopulmonary Exercise Test (peak VO_2)	• 6-min Walk Distance • 400m Walk Time
Lower Body Power	Function	Knee Extensor Power	• 1-Repetition Maximum
Muscle Mass	Biospecimen or Imaging	Urinary D3 Creatine Dilution	• CT muscle volume • MRI muscle volume
Muscle Summary Score – exceed threshold for % improvement in 2 out of 3 measures			

HOW TO WIN: HEALTHSPAN GRAND PRIZE

COGNITIVE			
Subdomain	**Type**	**Optimal Measure**	**Acceptable Measure**
Cognitive Summary Score	Function	NIH Toolbox Fluid Composite (executive function, attention and processing speed, working memory)	CanTab / Cambridge Cognition (executive function, attention and processing speed, memory)

Cognitive Summary Score – exceed threshold for % Fluid Cognition Composite OR improvements in >50% of selected cognitive function tests

NOTE: Additional tests could be named (e.g. sensory, mood). Biofluid-based biomarkers may be measured at a central lab should these be clinically validated for use in trials by time of Finals start

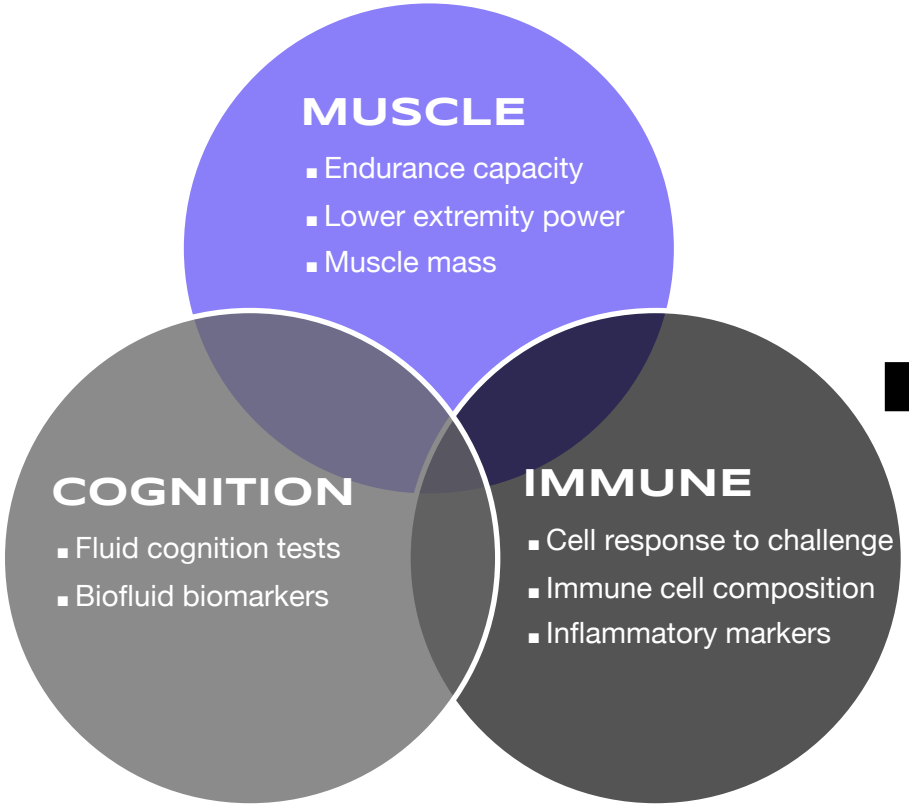
HOW TO WIN: HEALTHSPAN GRAND PRIZE

IMMUNE			
Subdomain	**Type**	**Optimal Measure**	**Acceptable Measure**
Response to challenge	Biospecimen	*Ex vivo* naïve immune response to a new stimulus (e.g. yellow fever)	Cellular mediated immune response in stimulated PBMCs or response to vaccine
Immune cell composition	Biospecimen	IMM-AGE Score	CD4+ : CD8+ ratio and lymphocyte : neutrophil ratio
Inflammatory status	Biospecimen	'Multikine' multiplexed assays (e.g. SASP Index)	

Immune Summary Score – exceed threshold for % improvement in 2 out of 3 measures.

NOTE: IMMUNE ASSAYS LISTED ARE NOT FINAL. We will provide Standard Operating Procedures for biospecimen collections and assays will be performed centrally using banked specimen.

HOW TO WIN: HEALTHSPAN GRAND PRIZE



INTELLECTUAL PROPERTY & TEAM DATA

- Each Team must own or hold appropriate license rights to all technologies, methods, resources, and Intellectual Property included in competition
- Teams will retain ownership of their Intellectual Property they bring to the Competition
- All proprietary details submitted to XPRIZE by teams will remain strictly confidential unless clearly and specifically noted
- Data generated in pursuit of prize and submitted to the XPRIZE DCC for judging is held by XPRIZE. Teams may retain copy of their data and use for publications, patent filings related to their therapeutic, and commercialization, but must adhere to XPRIZE marketing and communications best practices.

05

XPRIZE HEALTHSPAN

HOW TO WIN: FSHD BONUS FINALS

QUALIFYING SUBMISSION

PURPOSE: first formal opportunity for teams to demonstrate their ability to compete in the $10M FSHD Bonus Prize competition

QUALIFYING SUBMISSION

Research
& Development

Milestone 1:

- $10M
- $2M FSHD

Approximately 12 pages

- Summary……1pg
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- Technical Application……5pg
- Study Timeline…….. 1pg
- Scalability / Accessibility…….. 1pg

\+ Human Subjects Safety, Resourcing Plan, Biohazard

HOW TO WIN: $10M FSHD BONUS PRIZE

FSHD Bonus Prize will focus on Facioscapulohumeral Muscular Dystrophy (FSHD) and will culminate in adjudication of the final bonus prize based on testing interventions in clinically approved genetically tested FSHD individuals aged 50-80 years

MUSCLE

- Muscle fat fraction, fibrosis, muscle mass or novel biomarkers
- Functional tests

The winning FSHD Bonus Prize team should show:

- a 10% reduction in muscle fat fraction, fibrosis or increased muscle mass using best practices in biomedical imaging OR an acceptable muscle-derived or circulating biomarker
- **AND** a 20% improvement in at least 3 of the functional tests, as deemed appropriate for the therapeutic intervention

HEALTHSPAN & FSHD BONUS PRIZES

- **Teams may register to compete in one or both prize tracks: FSHD Bonus Prize and XPRIZE Healthspan**
- Qualified Teams competing in the Healthspan Competition **can transfer to the FSHD Bonus track at no additional registration fee**, but must submit a letter of intent to transfer to XPRIZE for review by the FSHD Judging Panel
- Judging Panels for XPRIZE Healthspan and the FSHD Bonus Prize are independent of one another

THANK YOU TO OUR SPONSORS, ADVISORS, PARTNERS, AND TEAMS

XPRIZE.ORG/PRIZES/HEALTHSPAN

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SVP, Partnerships & Impact

PETER H. DIAMANDIS, MD
Founder, Chairman of the Board, XPRIZE

XPRIZE HEALTHSPAN | HEVOLUTION | SOLVE FSHD

XPRIZE Healthspan Study Design: Simple Crossover with Personalized Response Thresholds

Nicholas J. Schork, Ph.D.

TGen, a part of The City of Hope National Medical Center;
UCSD; Scripps Research; SJHC; Seraphina Therapeutics

1. Basic study designs
2. Personalized thresholds
3. Counting responders
4. Additional issues

ARDD Symposium Copenhagen: 8/26/2024

10 minutes + Q&A

XPRIZE Study Design: A Balance of Practicality, Fairness, Vision, and Rigor

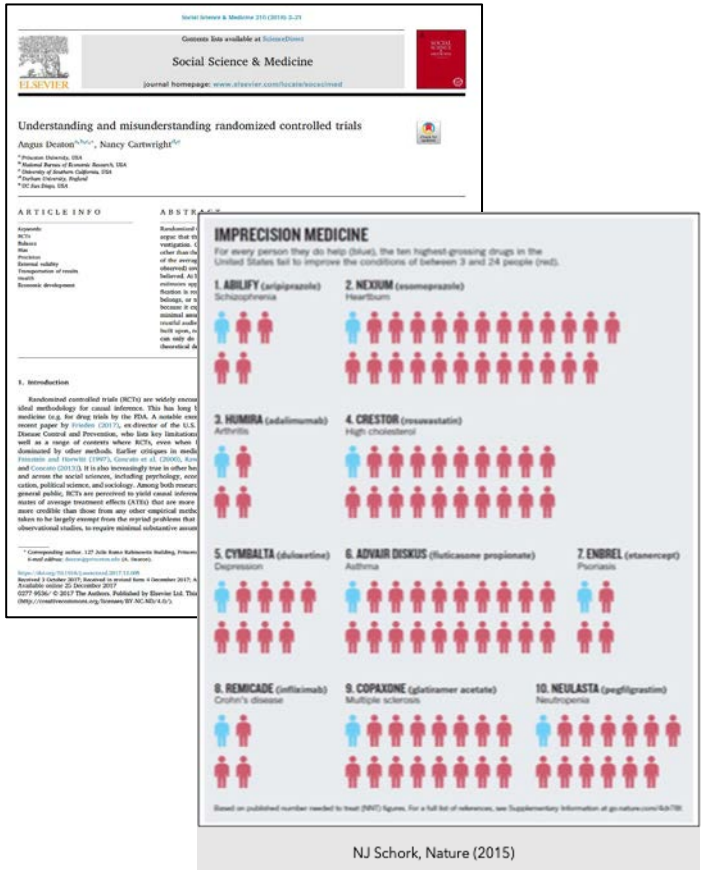
- Traditional RCTs are ideal for some inquiries, not so good for others
- Randomization doesn't always achieve the desired effect
- Matching subjects in Real Word Evidence (RWE) settings is being taken seriously by academics, pharma, and regulatory agencies

- Vetting 'precision' medicines requires complementary approaches
- Important distinctions in clinical trials for precision medicine:

  N-of-1 crossover and aggregated N-of-1 crossover trials
  Single Case Experimental Designs (SCEDs) and aggregated SCEDs
  Platform-based RCTs (test a platform precision medicine tech)
  The use of personalized thresholds to interpret responses

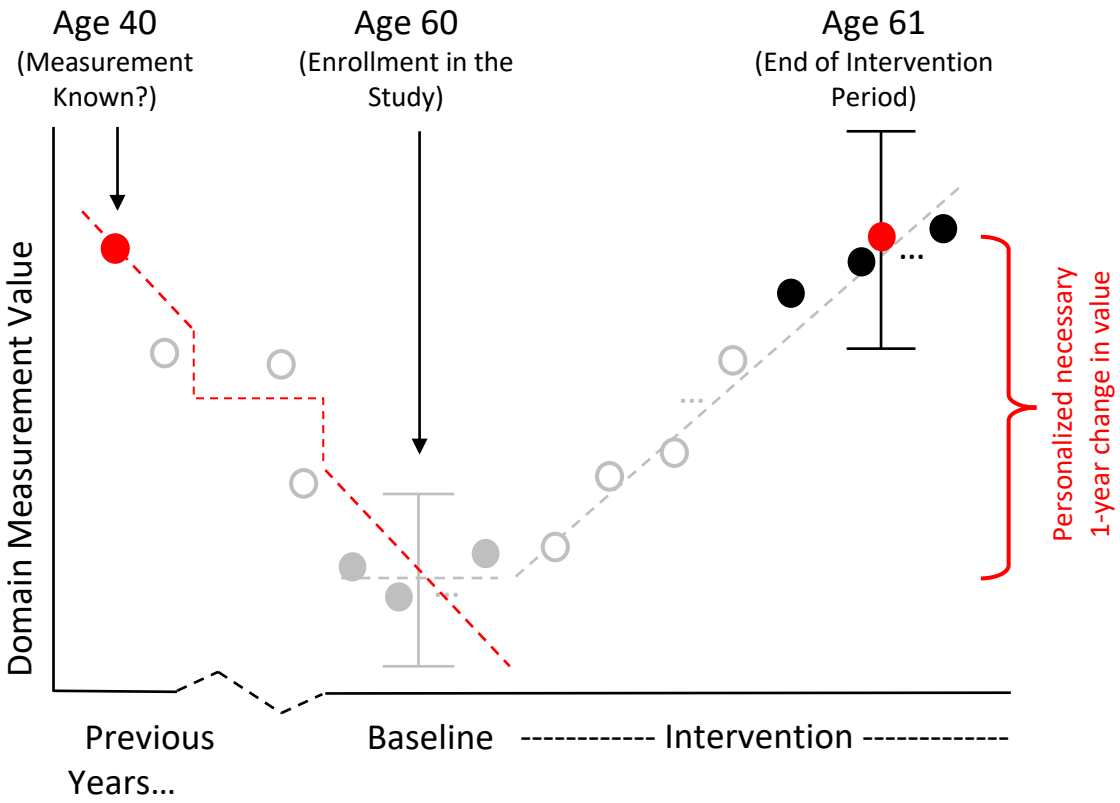
- XPRIZE Health Design:

  Crossover design with personalized thresholds as response criteria
  Count responders to determine efficacy
  Covariates and control groups can be considered in assessing efficacy
  Meta-analyses of the trials can be pursued to find distinguishing characteristics of the most efficacious interventions



NJ Schork, Nature (2015)

Personalized Response Thresholds and Criteria

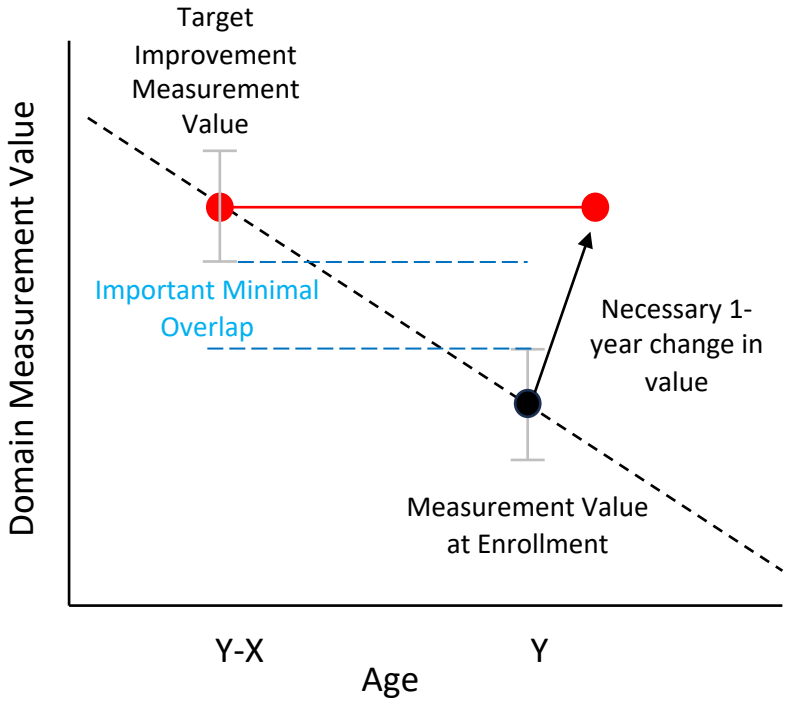


- Averages of 3 measurements pre and post intervention
- Multiple component measurements in each domain

Questions:

- What specific domain measures?
- What data will be used to define appropriate ‘younger’ target values for individual participants?
- What covariates should be considered (sex? ancestry? etc.?)
- 21-year vs. 20-year change? Change from *enrollment* value…

Overlap in Measurement Variability at Target Ages Determines Ease of Response



Questions:

- What data can be used to define errors?
- What is an acceptable difference between enrollment and target measurement errors?
- How will the overlap affect power?

Example Personalized Response Threshold Data and Determination: VO2 Peak

Progress in Cardiovascular Diseases 63 (2020) 730–737

Contents lists available at ScienceDirect

Progress in Cardiovascular Diseases

journal homepage: www.onlinepcd.com

Age-related change in peak oxygen uptake and change of cardiovascular risk factors. The HUNT Study

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ARTICLE INFO

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14 September 2020
14 September 2020

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Cardiorespiratory fitness
Exercise test
Cardiopulmonary exercise testing
Exercise training
Primary prevention
Epidemiology

ABSTRACT

Background: Large longitudinal studies on change in directly measured peak oxygen uptake (VO_{2peak}) is lacking, and its significance for change of cardiovascular risk factors is uncertain. We aimed to assess ten-year change in VO_{2peak} and the influence of leisure-time physical activity (LTPA), and the association between change in VO_{2peak} and change in cardiovascular risk factors.

Methods and results: A healthy general population sample had their VO_{2peak} directly measured in two (n = 1431) surveys of the Nord-Trøndelag Health Study (HUNT3; 2006–2008 and HUNT4; 2017–19).

Average ten-year decline in VO_{2peak} was non-linear and progressed from 3% in the third to about 20% in the eight decade in life and was more pronounced in men. The fit linear mixed models including an additional 2,033 observations from subjects participating only in HUNT3 showed similar age-related decline. Self-reported adherence to LTPA recommendations was associated with better maintenance of VO_{2peak}, with intensity seemingly more important than minutes of LTPA with higher age. Adjusted linear regression analyses showed that one mL/kg/min better maintenance of VO_{2peak} was associated with favorable changes of individual cardiovascular risk factors (all $p \leq 0.002$). Using logistic regression one mL/kg/min better maintenance of VO_{2peak} was associated with lower adjusted odds ratio of hypertension (OR 0.95 95% CI 0.92 to 0.98), dyslipidemia (OR 0.92 95% CI 0.89 to 0.94), and metabolic syndrome (OR 0.86 95% CI 0.83 to 0.90) at follow-up.

Conclusions: Although VO_{2peak} declines progressively with age, performing LTPA and especially high-intensity LTPA is associated with less decline. Maintaining VO_{2peak} is associated with an improved cardiovascular risk profile.

Cardiovascular disease (CVD) is a burden to societies and health-care systems globally despite the reduction in CVD mortality over the last decades,[1,2] and strategies for population-level prevention of CVD should have high priority. Low cardiorespiratory fitness (CRF) is a strong predictor of morbidity and mortality from both CVD and other causes.[3,4] Furthermore, it is a predictor of dependence,[5] which is of interest given the aging populations in most countries. The growing knowledge of CRF as a powerful composite health measure in both clinical and apparently healthy populations was highlighted in the 2016 recommendations for cardiopulmonary exercise testing (CPET) by the European Association for Cardiovascular Prevention & Rehabilitation and the American Heart Association.[3] To exploit the potential of CRF in both preventive and clinical settings knowledge about reference values and normal age-related changes in CRF is needed.

In a sub-study of the third wave of the Nord-Trøndelag Health Study (HUNT3, 2006–2008) peak oxygen uptake (VO_{2peak}) was assessed by CPET in 4631 apparently healthy men and women, establishing a large reference material on VO_{2peak}.[7] Reference values from the Norwegian HUNT population and several other populations have shown that normal CRF values differ widely across various populations.[7–9]

Knowledge on the age-related decline in CRF is important for follow-up of patients in lifestyle interventions and for identification of

Abbreviations: ACLS, Aerobics Center Longitudinal Study; BMI, Body mass index; BP, Blood pressure; CARDIA, Coronary Artery Risk Development in Young Adults; CPET, Cardiopulmonary exercise testing; CRF, Cardiorespiratory fitness; CVD, Cardiovascular disease; HbA1c, Glycosylated hemoglobin; HDL, High-density lipoprotein cholesterol; HR, Heart rate; HUNT, Nord-Trøndelag Health Study (Helseundersøkelsen Nord-Trøndelag); LTPA, Leisure-time physical activity; PA, Physical activity; VO_{2peak}, Peak oxygen uptake; WC, Waist circumference.

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E-mail address: bjarne.nes@ntnu.no (B.M. Nes).

https://doi.org/10.1016/j.pcad.2020.09.002
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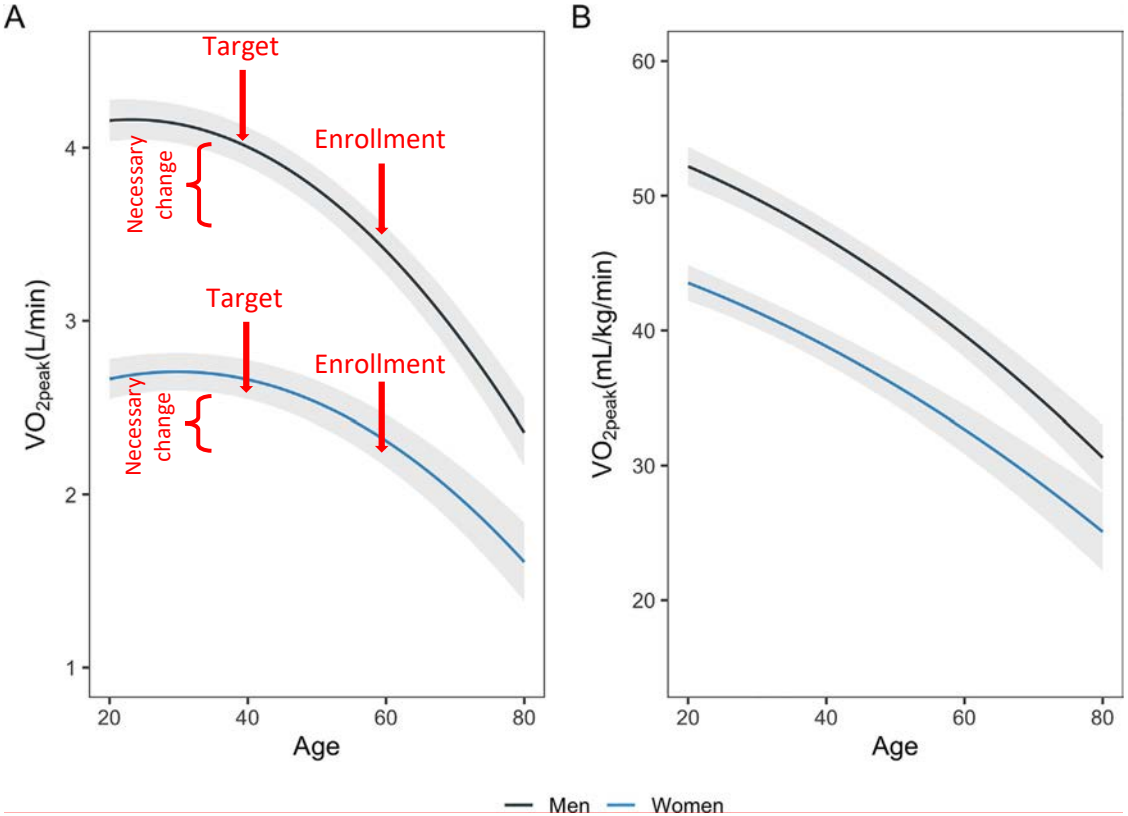
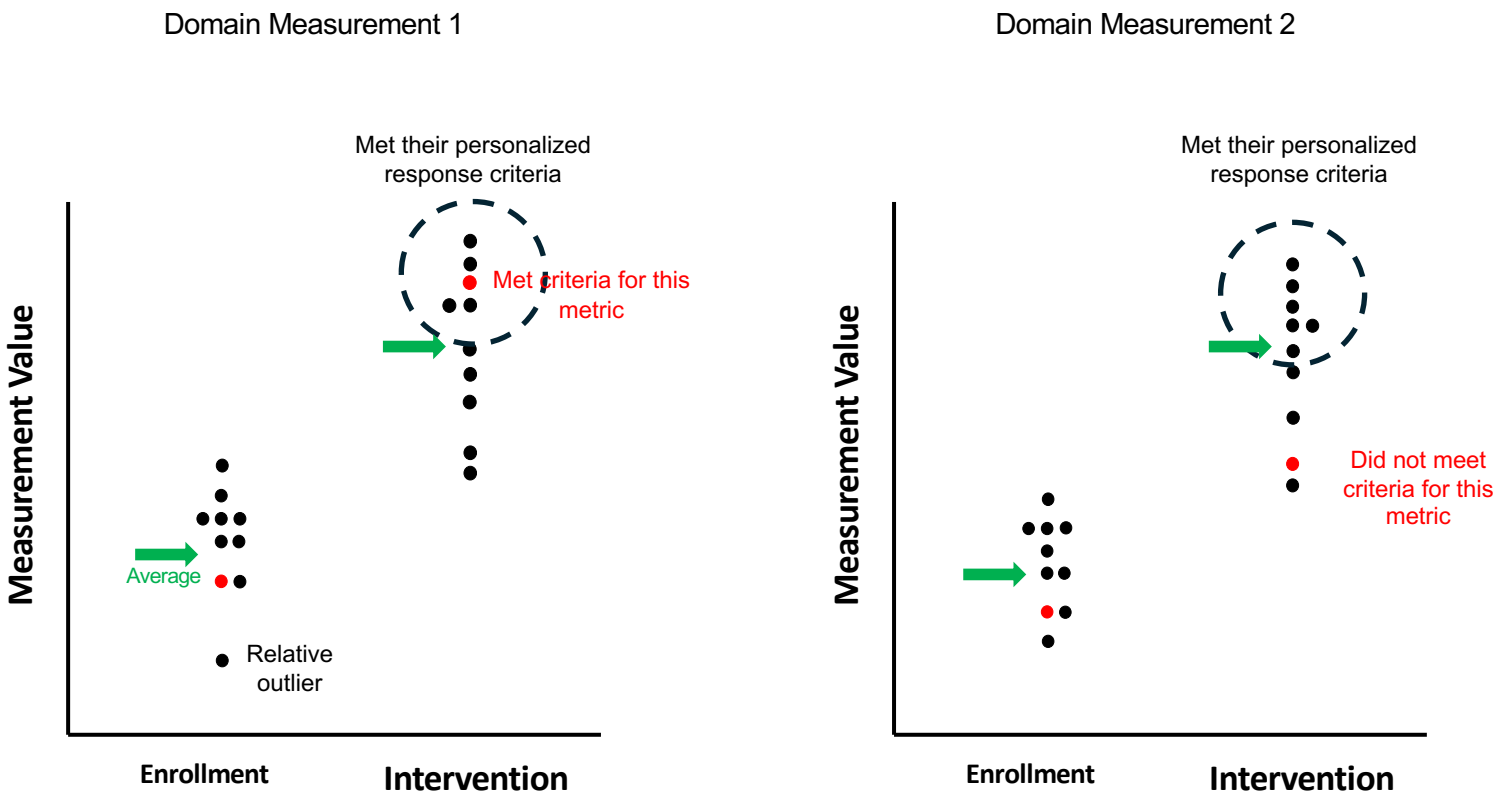


Counting Individual Responders vs. Looking at Average Measurement Changes



To be considered a responder a participant must meet personalized criteria for the different domains

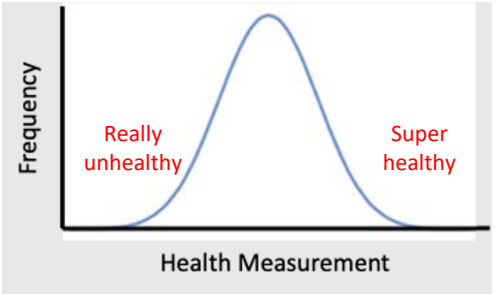
Use of Control Groups and Potential for Biased Enrollment

Control Groups

Outcome	Control	Intervention
Responders	$f_{r,c}$	$f_{r,i}$
Non-responders	$f_{n,c}$	$f_{n,i}$

- Want to see $f_{r,I} >> f_{r,c}$
- Control rates from epi data defining thresholds
- Placebo or natural history study data?
- Exercise as a control intervention?

Biased Enrollment



- Enrolling super healthy people means they need to get even healthier on the intervention (-10/20 years?)
- Reducing multiple morbidities may be difficult if pathological remodeling has occurred

Additional Analysis Methods/Constructs That Could Be Exploited:

- Random Effects meta-models aggregated all trial data
- Meta-analyses of trial results summaries
- Competition-wide control of type I error rates (e.g., Bonferroni correction)

How Long Does it Take to Remodel the System and Induce Health Benefits?

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Viewpoint

Does Modulation of an Epigenetic Clock Define a Geroprotector?

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ABSTRACT

There is growing interest in the development of interventions (e.g., drugs, diets, dietary supplements, behavioral therapies, etc.) that can enhance health during the aging process, prevent or delay multiple age-related diseases, and ultimately extend lifespan. However, proving that such 'geroprotectors' do what they are hypothesized to do in relevant clinical trials is not trivial. We briefly discuss some of the more salient issues surrounding the design and interpretation of clinical trials of geroprotectors, including, importantly, how one defines a geroprotector. We also discuss whether emerging surrogate endpoints, such as epigenetic clocks, should be treated as primary or secondary endpoints in such trials. Simply put, geroprotectors should provide overt health and disease prevention benefits but the time-dependent relationships between epigenetic clocks and health-related phenomena are complex and in need of further scrutiny. Therefore, studies that enable understanding of the relationships between epigenetic clocks and disease processes while simultaneously testing the efficacy of a candidate geroprotector are crucial to move the field forward.

KEYWORDS: geroprotectors; the geroscience hypothesis; clinical trials; epigenetic clocks; biomarkers

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INTRODUCTION

The development of drugs, diets, activities, etc. that sustain health throughout the aging process, increase vitality and ultimately enhance longevity has been on the minds of humans for centuries [1–3]. Not only is this interest rooted in an innate individual desire to live a long and healthy life, but, more generally, there is a growing consensus among biomedical scientists that by identifying interventions that modulate some basic

Adv Geriatr Med Res. 2022;4(1):e220002. https://doi.org/10.20900/agmr20220002

- What about acute vs. long term health benefits?
- Aging rate measurements (e.g., epigenetic clocks, omics-based clocks, functional rate of decline, etc.) *could* reflect geroprotector benefits
- If a geroprotector works, it must have a ripple effect on ALL or MOST systems that, when compromised, lead to morbidities and mortality
- How long it takes before a geroprotector sinks in, slows, e.g., the clock, and ultimately remodels relevant systems for the better are crucial questions!
- Without observable acute effects on clinically-relevant measures, what is the long-term (however defined) mechanism of action (MOA)?

"In fact, the question of how long it might take for a geroprotector to induce health benefits could lead to the almost comical, yet likely true, claim that one could literally die of age-related diseases while waiting for their geroprotector to induce its favorable effects!" (page 7)

Simple Crossover Design with Personalized Response Criteria

Figure 1. Schematic for Defining Target Improvements in the 3 Domains.

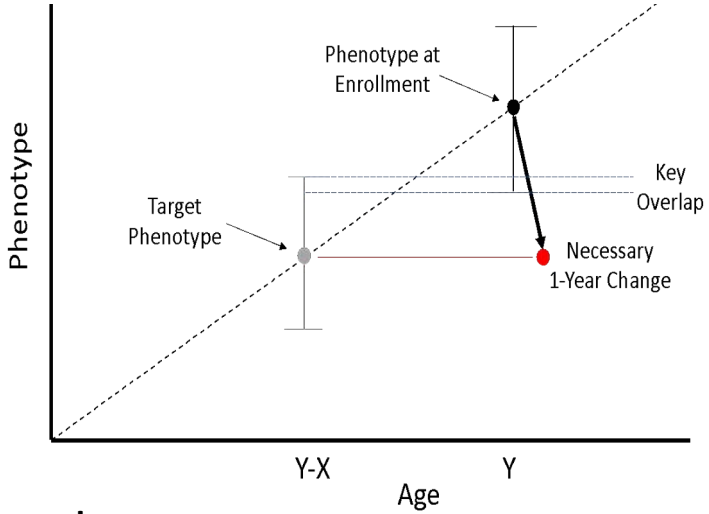
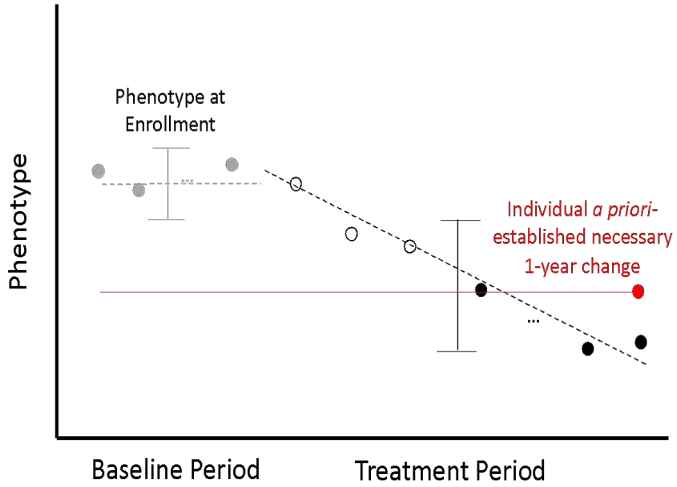


Figure 2. Schematic Depicting the Repeated Measurements on Individuals and Their Use in Determining Necessary Improvements



Key Elements:

- Need to define the necessary change for each person: an x-year reduction based on population data or a percent change?
- Individuals must show measurement values equal to/less than their necessary 1-year change for each (?) domain to count as responders
- Control groups (using randomization?) to establish expected frequency of spontaneous responders (all controls should be equal)
- No advantages for enrolling super healthy or super unhealthy people since each enrollee has a personalized target improvement of x years based on their phenotype at enrollment
- Balance feasibility and rigor using stringent necessary, and unlikely spontaneous, changes for each individual; controls for covariate effects
- Winner based on statistical comparisons with control group frequencies and also greatest relative frequency of responders?

XPRIZE HEALTHSPAN | HEVOLUTION | SOLVE FSHD

SOLVE FSHD

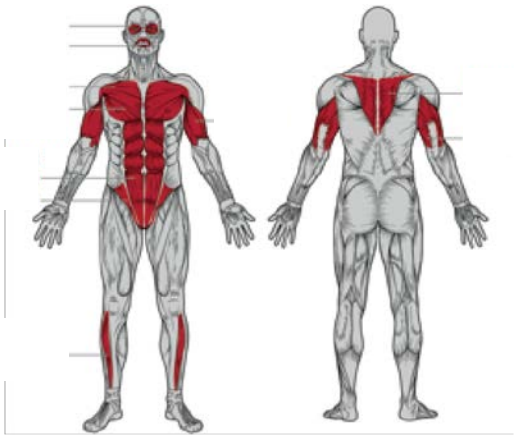
Our Mission

- We are mission-focused on finding a cure for FSHD by 2027
- Seeking to accelerate the pace of innovation and remove barriers to finding a cure using cutting-edge technologies and traditional approaches
- Supporting our partners through strategic investments, our internal drug development experience, and access to a world class global scientific and drug development network

WHAT IS FSHD?

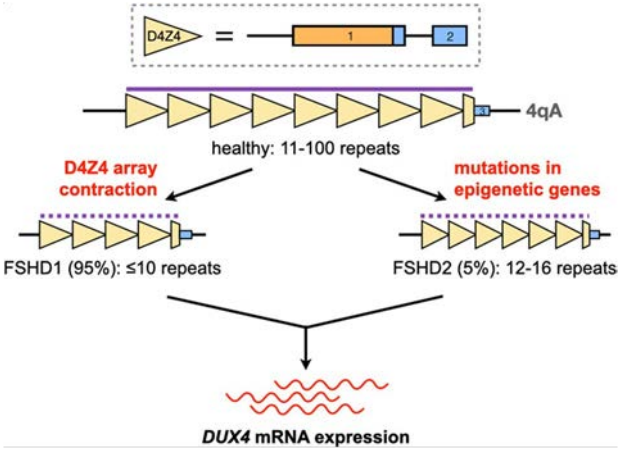
FSHD is a Rare Form of Muscular Dystrophy

- Progressive muscle degeneration and weakness leads to an inability to lift objects, groom oneself and walk



FSHD is Heterogeneous

- Genetic and epigenetic causes
  - Deletions from D4Z4 region of chromosome 4
  - Hypomethylation of DNA in region

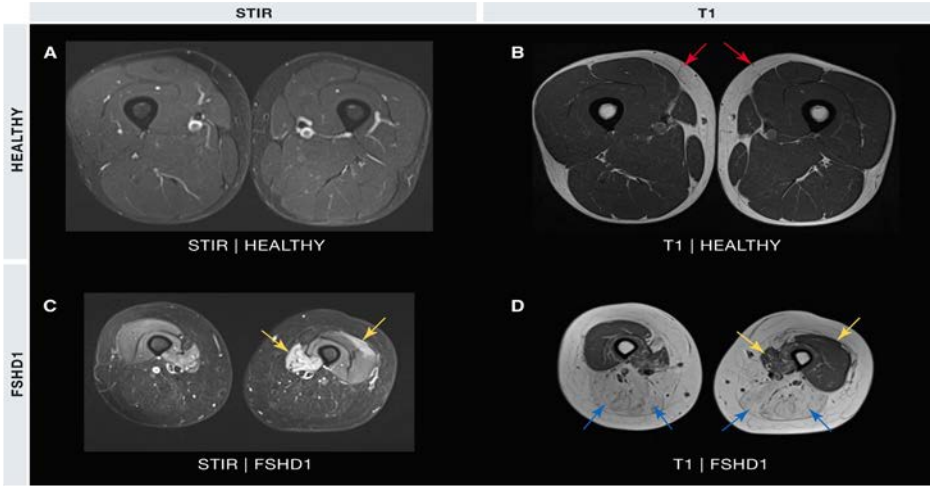


Aberrant DUX4 expression results in FSHD

Hallmarks of FSHD Pathology

FSHD is characterized by inflammation and fat infiltration in muscle

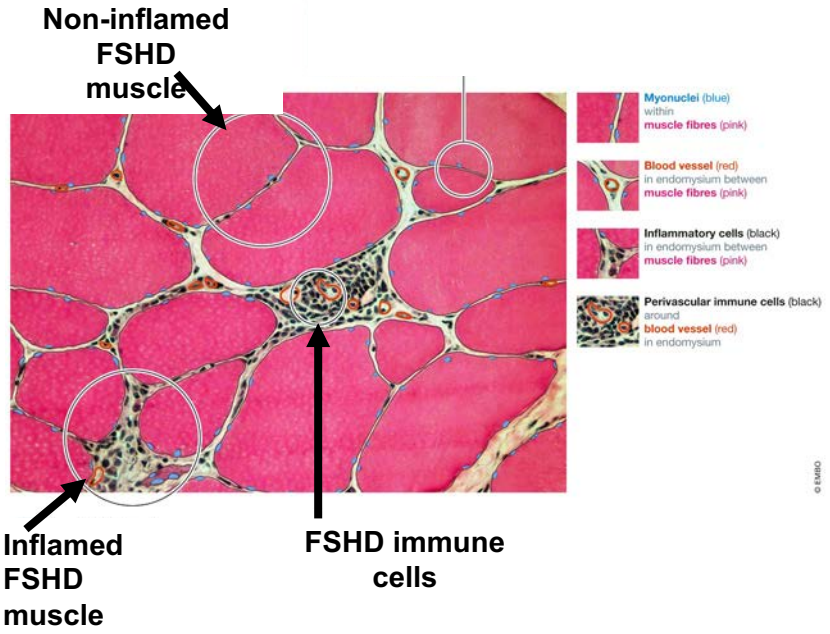
- FSHD muscle is characterized by STIR (Short Tau Inversion Recovery) positive MRI images indicating inflammation and bright T1 images reflecting fat infiltration
- Heterogeneity between and within muscles



Banerji and Zammit 2021 EMBO Mol Med 13: e13695

Hallmarks of FSHD Pathology

FSHD is characterized by inflammation and fat infiltration in muscle



Overlapping muscle pathology with sarcopenia

Banerji and Zammit 2021 EMBO Mol Med 13: e13695

UNDERSTANDING FSHD

FSHD BONUS PRIZE CRITERIA

A Bonus Prize of $8,000,000 will be awarded to the First Place Team

Must demonstrate an improvement from baseline that exceeds:

- A 10% reduction in muscle fat fraction using an appropriate imaging method OR an acceptable muscle-derived or circulating biomarker
- A 20% improvement in at least 3 functional tests from relevant clinical outcomes assessment, such as, but not limited to:
  - 6 minute walk test (6 MWT)
  - Gait speed (GS)
  - Grip test (GT)
  - Knee extensor maximum voluntary contraction (MVC)
  - Timed up and go (TUG)
  - Revised Upper Limb Module (RULM)
  - FSHD-COM (complete test or select components)
  - Reachable Workspace (RWS)
  - Novel functional endpoint as a clinical outcome assessment for FSHD

FSHD BONUS PRIZE CRITERIA

FSHD Composite Outcome Measure

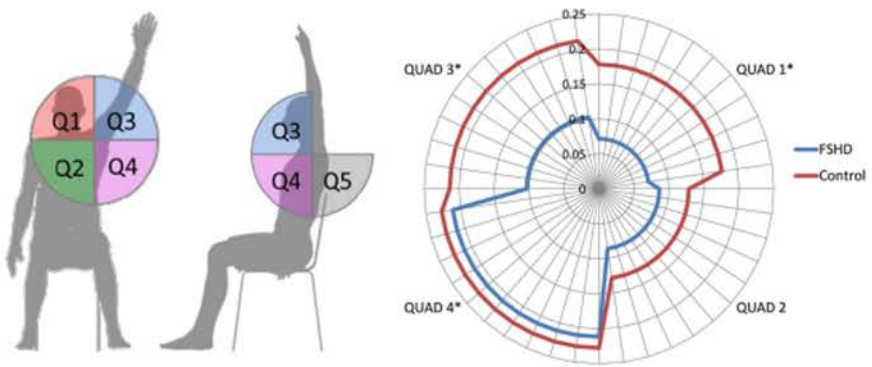
	ITEM	Score 0	Score 1	Score 2	Score 3	Score 4	References
LEG FUNCTION	Sit to stand	≤1 sec	1.1–2 sec	2.1–3 sec	>3 sec	Unable	18,19
	6 MWT	≥650 m	649–518 m	517–386 m	385–254 m	≤253 m	20,21
	Self-selected gait speed	≥139 cm/sec	138.9–123 cm/sec	122.9–107 cm/sec	106.9–89 cm/sec	<88.9 cm/sec	23,24
	Go 30′	≤4 sec	4.1–8 sec	8.1–12 sec	>12 sec	Unable	25,7
	Ascend/descend stairs	≤2 sec	2.1–4 sec	4.1–6 sec	>6 sec	Unable	9,25,7
ARM/SHOULDER FUNCTION	Shoulder Abduction (R/L)	2kg weight above head	Antigravity	≥ 90 degrees	<90 degrees	<45 degrees	9,26,25
	Shoulder Forward Flexion (R/L)	2kg weight above head	Antigravity	≥ 90 degrees	<90 degrees	<45 degrees	26,25,9
	Elbow Flexion (R/L)	3kg weight	Antigravity	≥90 degrees	<90 degrees	<10 degrees	26,25,9
	Don/doff Coat	≤10 sec	10.1–15 sec	15.1–20	>20	Unable	27
TRUNK FUNCTION	Pick up a penny from floor	≤2 sec	2.1–4 sec	4.1–6 sec	>6 sec	Unable	27
	Sit up with feet held	Able to do fully	Able to rise >45 degrees	Able to bring shoulders off	Only able to lift head off	Unable	2
	Supine to sit	≤3 sec	3.1–6 sec	6.1–9 sec	>9	Unable	2,33
HAND FUNCTION	Hand Grip Force Men	Both ≥ 35 kg	1 side <35 kg	1 side < 25 kg, or 2 sides < 35 kg	1 side < 20 kg, or 2 sides < 25 kg	1 side < 15 kg, or 2 sides < 20 kg	6,7,29,30
	Hand Grip Force Women	Both ≥ 23 kg	1 side <23 kg	1 side < 17 kg, or 2 sides < 23 kg	1 side < 14 kg, or 2 sides < 17 kg	1 side < 11 kg, or 2 sides < 14 kg	6,7
BALANCE	TUG: Timed up and Go	<6 sec	6–8 sec	8.1–10 sec	10.1–12 sec	<12 sec	32,33

R=right, L=left.

Eichinger et al. 2019 Muscle Nerve

Reachable Workspace Enables Quantification of Disease Progression

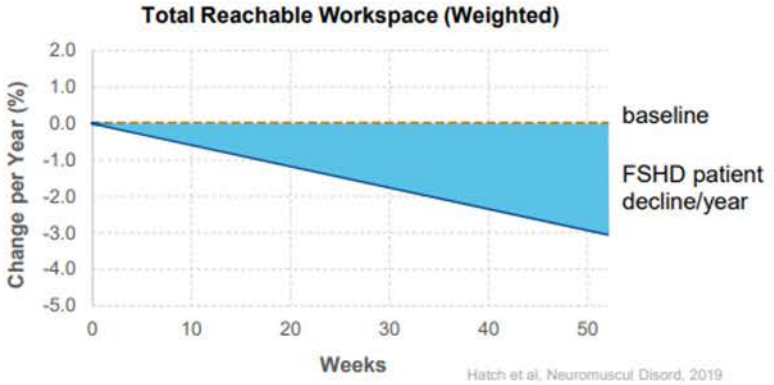
RWS measures global upper extremity function



Han et al, Muscle Nerve, 2015

- Reachable Workspace (RWS) is a quantification of upper limb motion utilizing a contactless sensor-based system
- RWS is evaluated using a series of protocol-directed arm motions (with and without weights) assessing Relative Surface Area (RSA) across five quadrants (Q1-Q5)
- RSA has been shown to correlate with abilities to perform activities of daily living (e.g., eating, self-care)

FSHD natural history demonstrates a ~3% RWS decline year over year



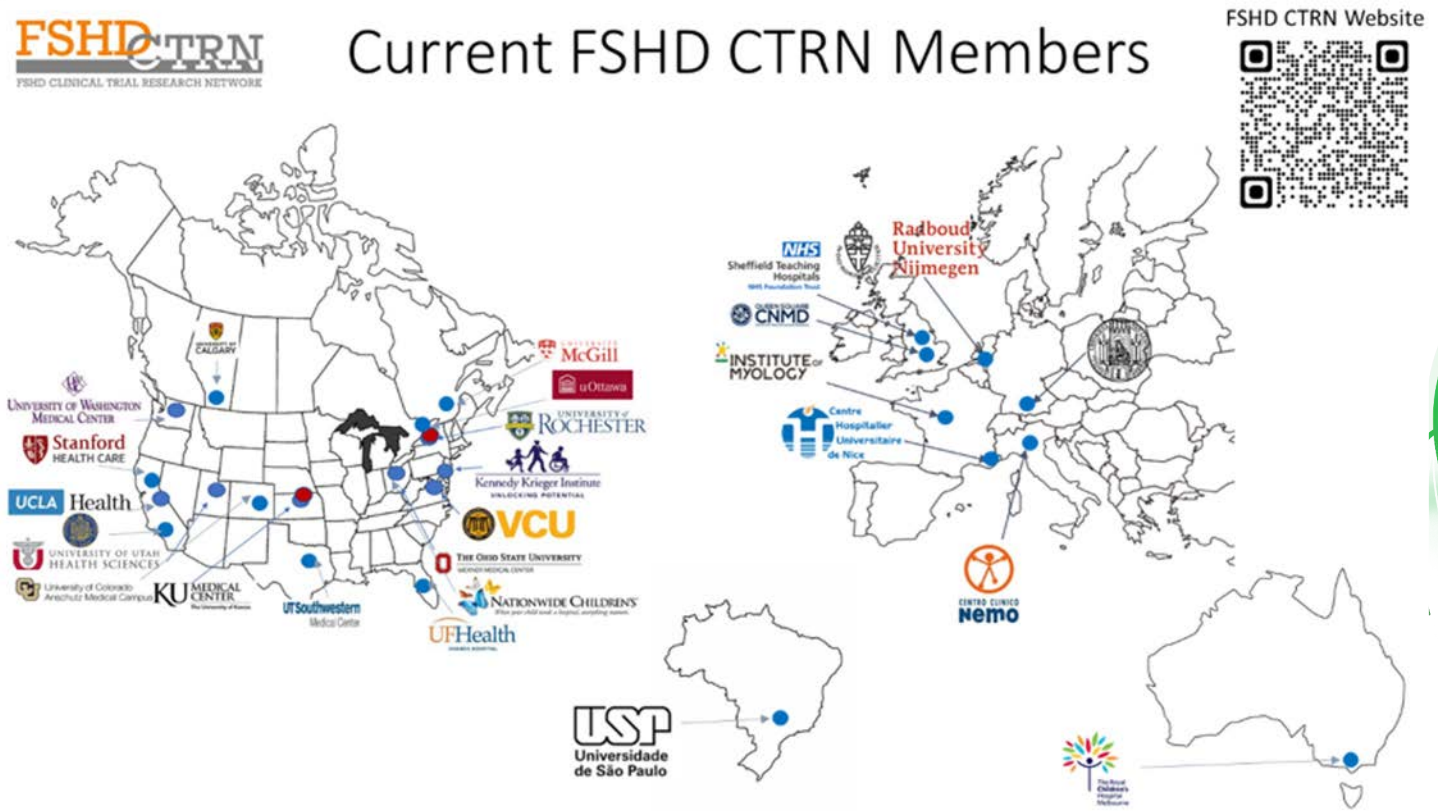
Hatch et al, Neuromuscul Disord, 2019

- Demonstrated sensitivity to disease progression in FSHD and in Duchenne/Becker muscular dystrophy
  - A longitudinal study in a FSHD patient population* exhibited annual declines in RWS of ~3% (measured Q1-Q4) compared to baseline

RWS: Reachable workspace. Han et al, Muscle Nerve, 2014; Han et al, Muscle Nerve, 2015; Hatch et al, AAN Annual Meeting, 2022; Hatch et al, Neuromuscul Disord, 2019; Kurillo et al, Technol Health Care, 2013; Mellion et al, AAN Annual Meeting, 2022
*N=16 patients

FSHD BONUS PRIZE RESOURCES

Clinical Trial Research Network



FSHD IS PRIMED FOR INNOVATION

1 Well Characterized Disease Biology

- Putative cause of FSHD is increased expression of DUX4

2 Tractable Target

- DUX4 expression is well suited for inhibition

3 Engaged Patient and Physician Community

- Global patient advocacy groups, respected KOLs

4 Potential for Rapid Clinical Development

- Existing and growing patient registries
- Established regulatory pathway

5 Sizeable Commercial Opportunity

- No current standard of care

❖ ***Estimated patient population of 16,000 to 38,000 in the U.S. and 35,000 in Europe***

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02

MEASURING MUSCLE, COGNITIVE, AND IMMUNE FUNCTION

MEASURING MUSCLE, COGNITIVE, AND IMMUNE FUNCTION

STEVE CUMMINGS, MD
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University of Connecticut

Muscle Endpoints

Steve Cummings, MD

San Francisco Coordinating Center
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Dept. of Epidemiology and Biostatistics,
U.C. San Francisco

Optimal Endpoint Measurements

Subdomain	Type	Optimal Measure
Endurance Capacity	Function	Cardiopulmonary Exercise Test (peak VO_2)[32]
Lower Body Power	Function	Knee Extensor Power or rate of torque development (RTD)[35]
Muscle Mass	Biospecimen or Imaging	Urinary D3 Creatine Dilution[37, 38]

Acceptable Endpoint Measurements

Subdomain	Type	Optimal Measure	Acceptable Measure
Endurance Capacity	Function	Cardiopulmonary Exercise Test (peak VO_2)[32]	• 6-min Walk Distance[33] • 400m Walk Time[34]
Lower Body Power	Function	Knee Extensor Power or rate of torque development (RTD)[35]	• 1-Repetition Maximum[36]
Muscle Mass	Biospecimen or Imaging	Urinary D3 Creatine Dilution[37, 38]	• CT muscle volume[39, 40] • MRI muscle volume[38]

Competitors will be expected to use optimal measurements unless an exception is made because the optimal measurement is not feasible

Sources of Data

Baltimore Longitudinal Study of Aging (BLSA)

- Longitudinal study since 1958, now ~1600 ages 20+
- Periodic intensive measurements of muscle

Study of Muscle Mobility and Aging (SOMMA)

- 879 participants age 70+ years with muscle biopsies to assess mitochondrial function, and extensive measurements of muscle and mobility

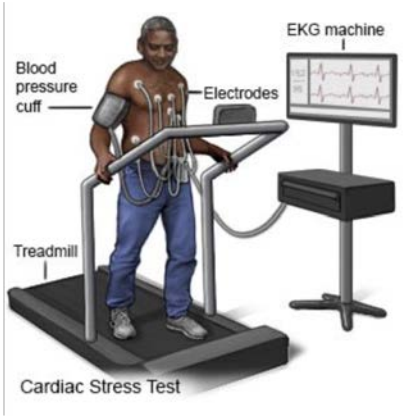
Endurance capacity

Optimal: VO_2 peak

Acceptable: 400m and 6-minute walks

VO_2 Peak*

- Measures oxygen consumption during standard standard exercises
- Treadmill or cycle
- Increasing intensity to maximum tolerable level
- Predicts disability & mortality

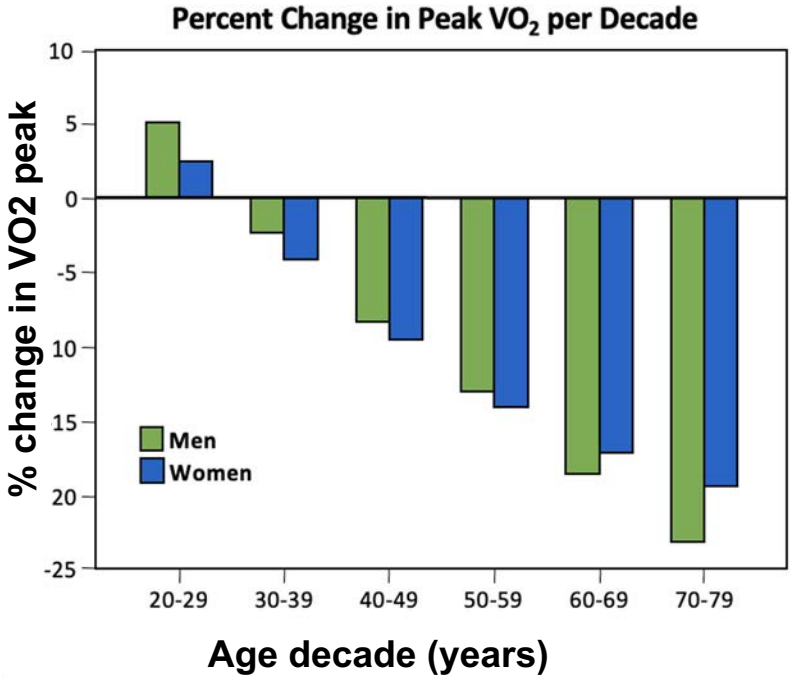


*Similar to VO_2max

Alexander JGMS 2003;58(8):734-9

VO_2 Peak Declines With Age

- Women and men ages 21 to 87 years from BLSA
- Median 8 years follow-up
- The rate of decline in VO2 peak increases with age



Fleg, Circulation. 2005;112:674-682.sd

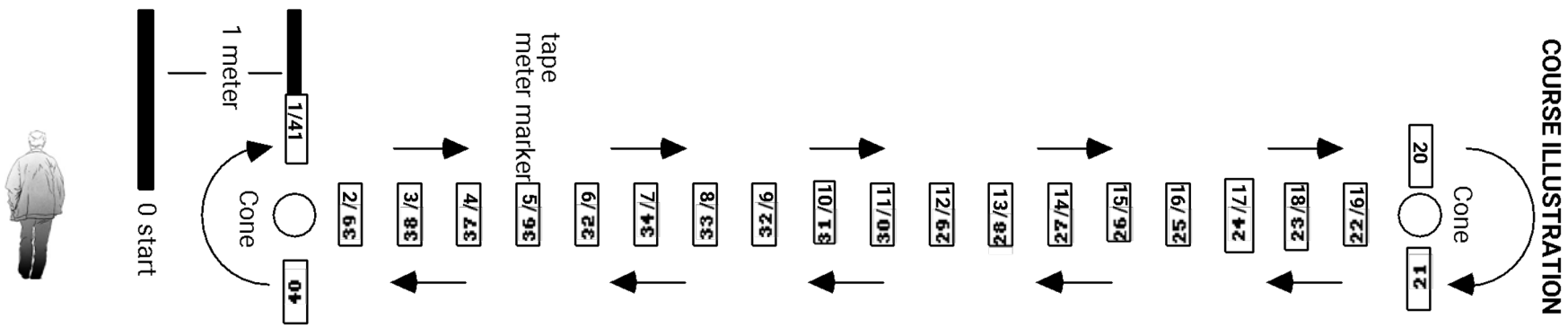
Treatment Target for VO_2 Peak

- VO_2 peak declines ~20% over 10 years
- Goal of 10-year restoration of function: Gain ~ 20% VO_2 peak
- Meta-analysis: Over 60 years old, exercise training >20 weeks results in ~ 16% improvement in VO_2 peak

Fleg, Circulation. 2005;112:674-682.sd

400m Walk Time

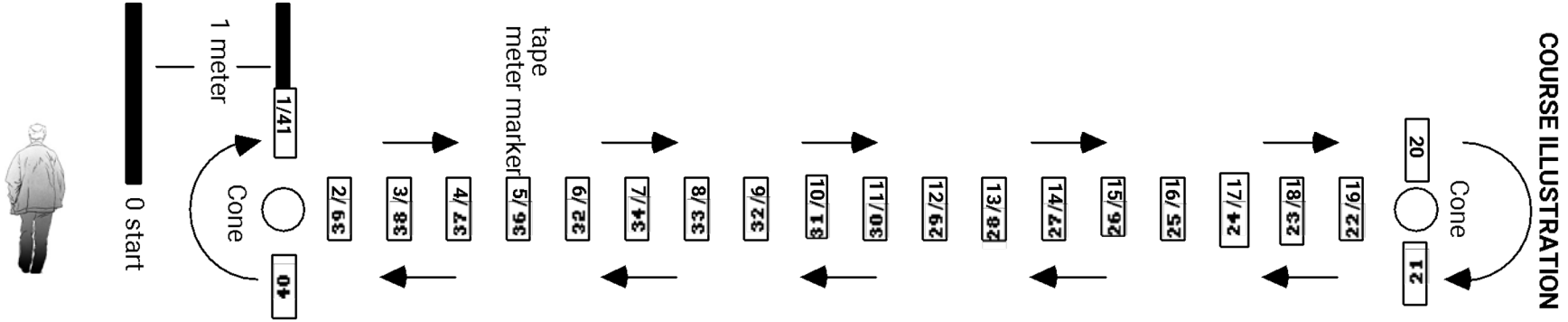
- For example, 10 circuits of a 40-meter course
- Fast 400m walk: As fast as you can safely walk
- Time required to complete 400 meters



Simonsick et al. J Am Geriatr Soc 54:127–132, 2006.

400m Walk Time

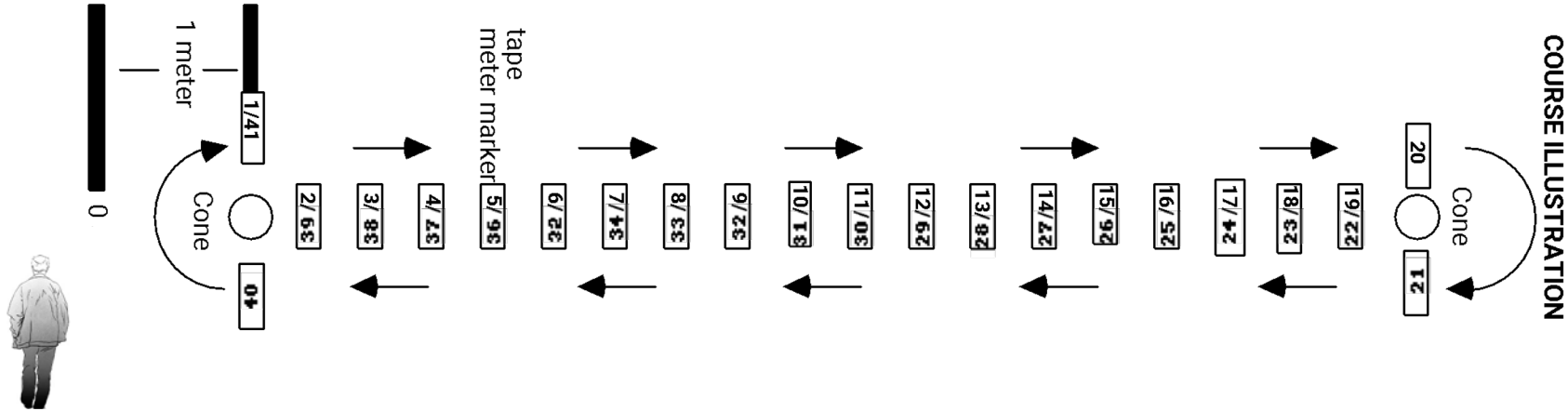
- Mobility disability: inability to walk 400m in 15 minutes
- Common endpoint of clinical trials



Simonsick et al. J Am Geriatr Soc 54:127–132, 2006.

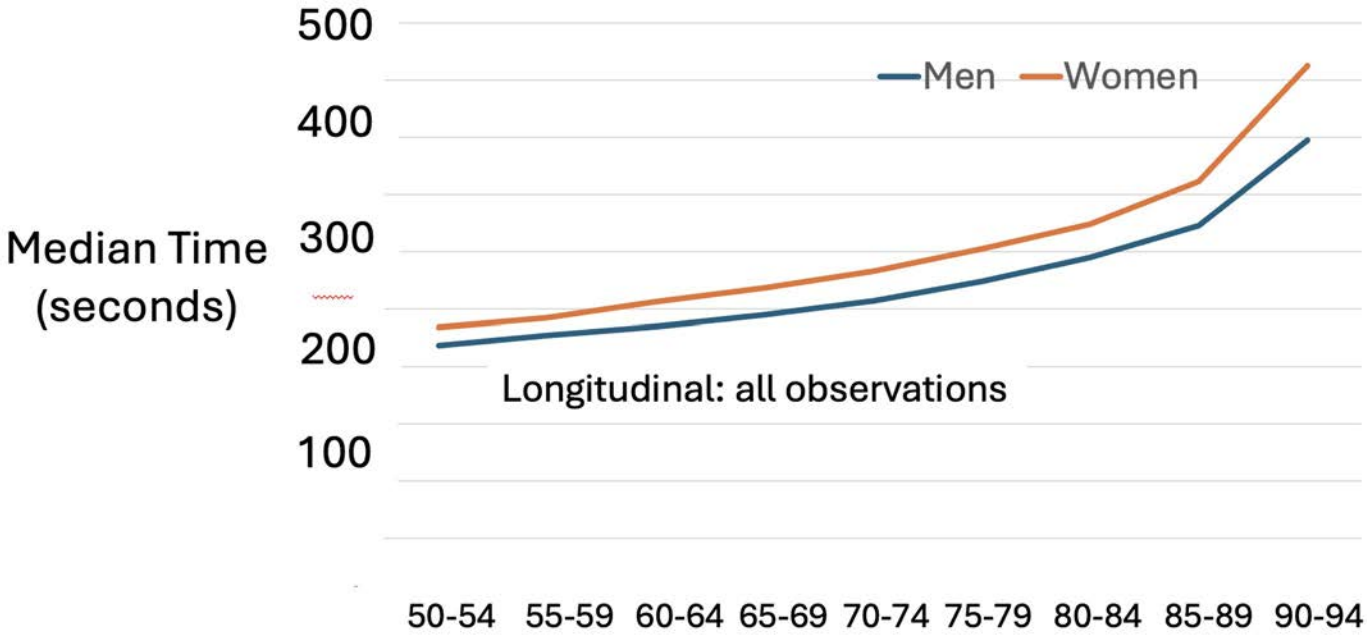
6-minute Walk Distance

- How far can you walk in 6 minutes
- Commonly used as and endpoint in studies and trials for cardiopulmonary disease



Simonsick et al. J Am Geriatr Soc 54:127–132, 2006.

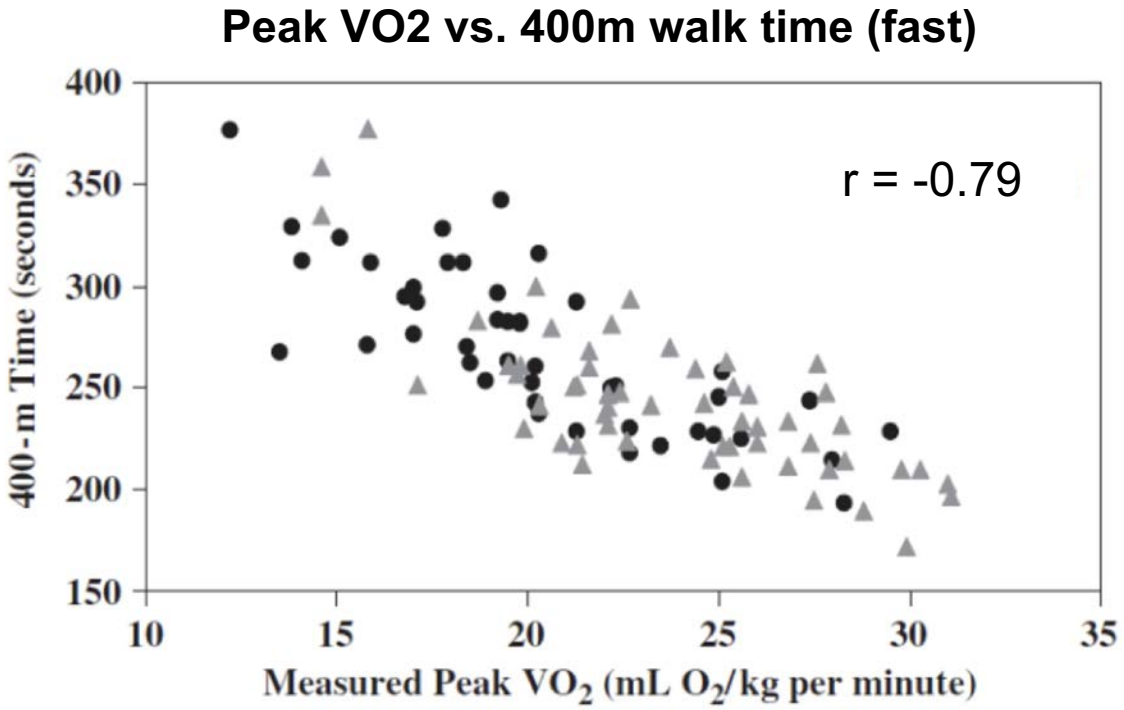
Fast 400m Walk Time Increases With Age



From Eleanor Simonsick. BLSA

*Test failures were assigned 900 seconds

Optimal vs. Acceptable Measure



Simonsick et al. J Am Geriatr Soc 54:127–132, 2006

Lower Body Power

Optimal: Power

Acceptable: Strength

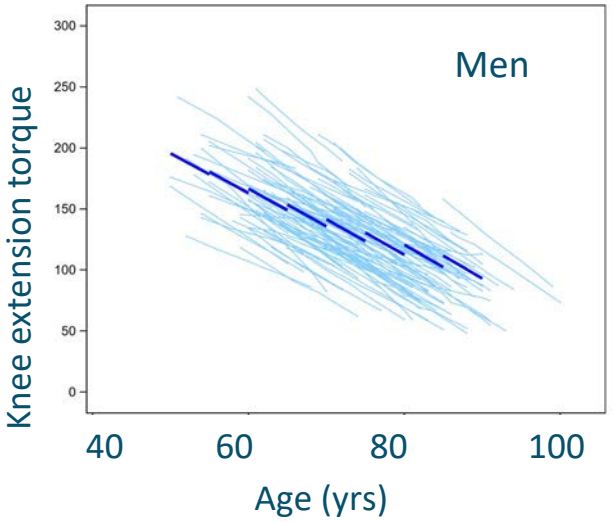
Muscle Power and Strength

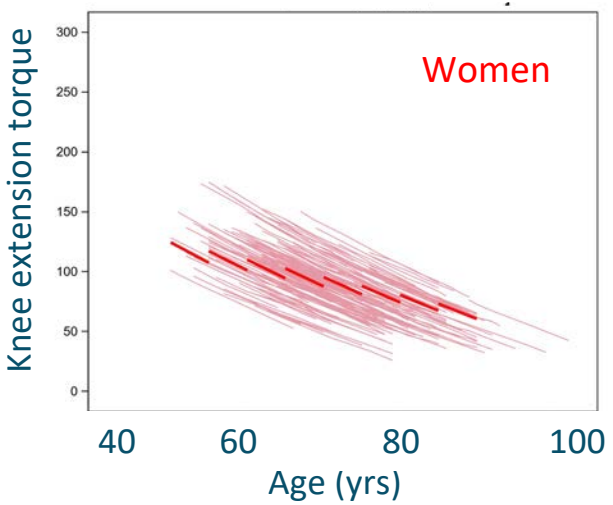
- Muscular **power** is the ability to exert maximal force quickly
- Muscular **strength** is the ability to exert maximal force
- Must be measured by a leg dynamometer*

*Hand-held dynamometers are poorly reproducible and depend on examiner and participant effort

Power and Strength Decrease with Age

- Longitudinal data from BLSA
- Men are stronger than women but percent change per decade is similar
- 15% change in peak torque per decade
- 20-year goal XPRIZE goal: about 30% improved power





BLSA

Muscle Mass

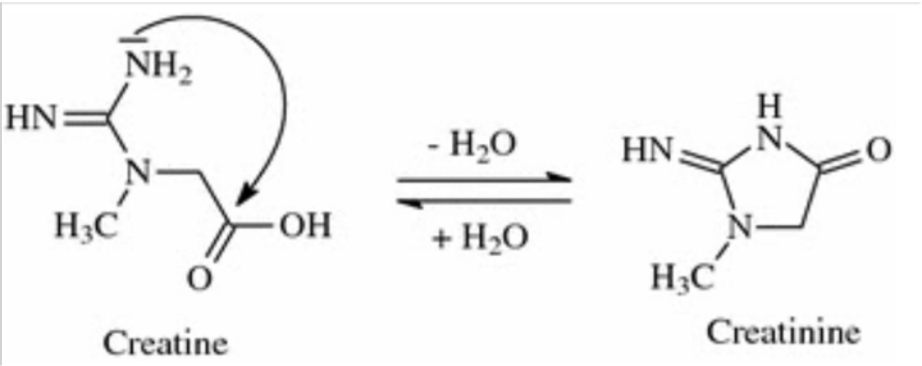
Optimal: D3 Creatine Dilution (D3Cr)

Acceptable: Leg muscle volume by MR or CT

What is D3 Creatine Dilution?

Creatine in Muscle is Converted to Creatinine

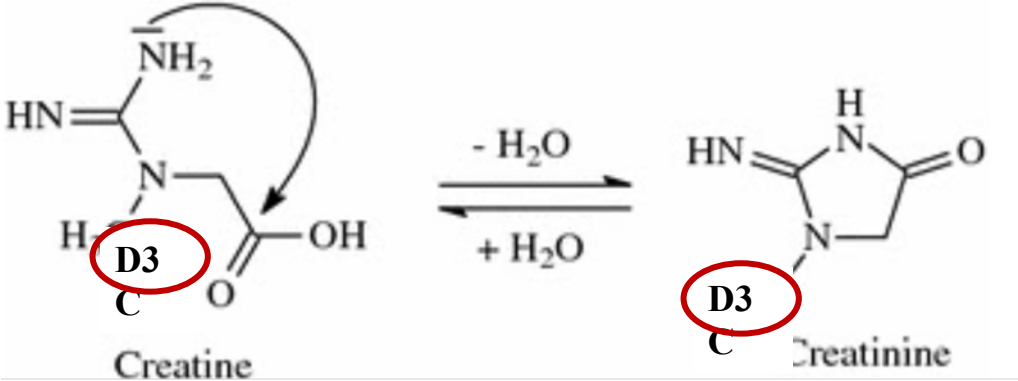
- Creatine from diet is taken up in muscle
- Creatine is involved in transfer of P to generate ATP
- 98% of creatine is in skeletal muscle
- ~1.7% of creatine is converted to creatinine excreted in urine



Creatine Creatinine

The D3Cr Dilution Assay Estimates Total Skeletal Muscle

- Label Creatine with deuterium (D3)
- Drink a dose of D3Creatine
- D3 Creatinine is excreted in urine.
- Specimen of urine taken at ~3 days



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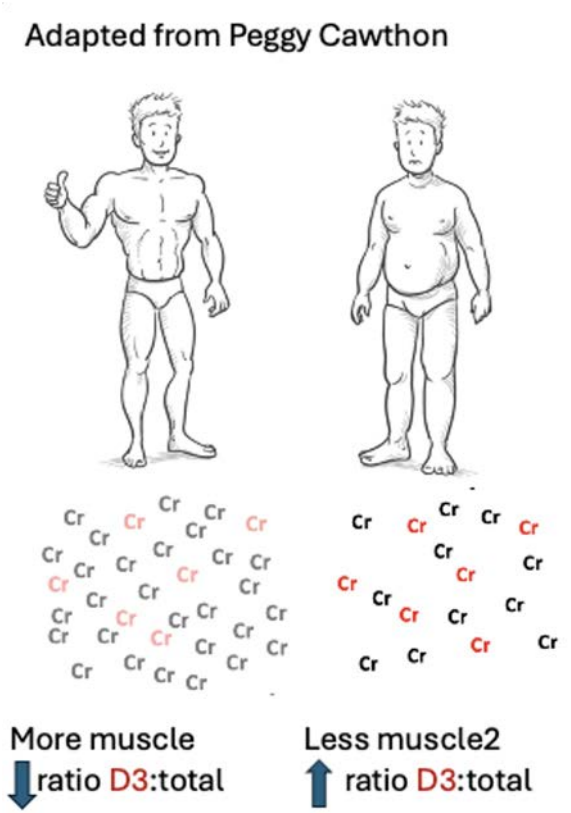
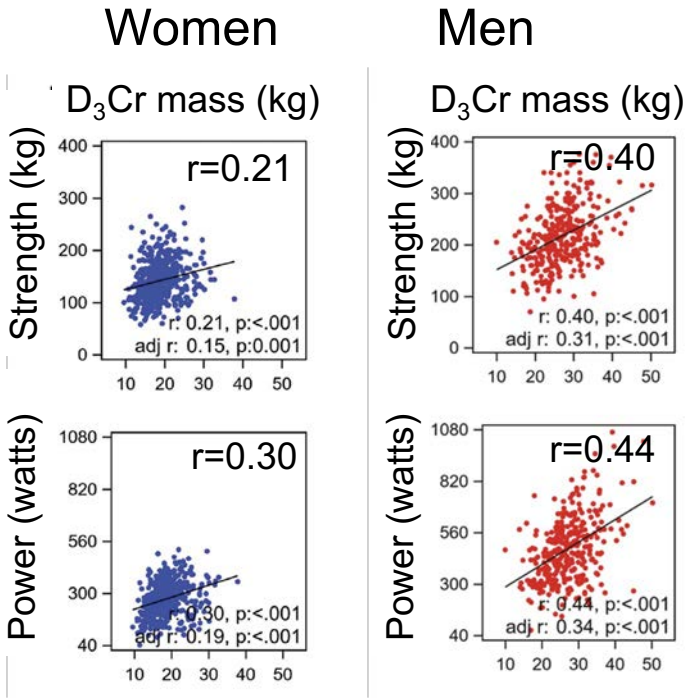
- Label Creatine with deuterium (D3)
- Drink a dose of D3Creatine
- D3 Creatinine is excreted in urine
- Specimen of urine taken at ~3 days
- A higher ratio of Cr to D3 Cr indicates higher muscle mass



Total Muscle Mass by D3Cr

- Total skeletal muscle mass by D3Cr is associated with leg power and strength
- Skeletal muscle mass by D3Cr is associated with disability, falls, fractures…

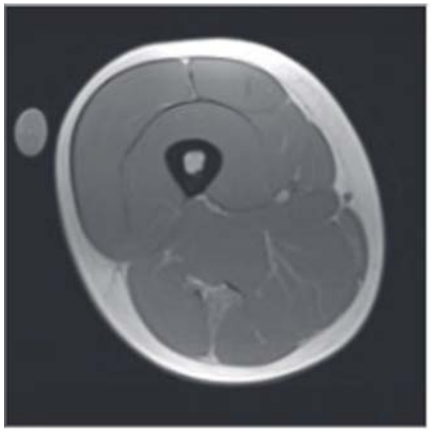


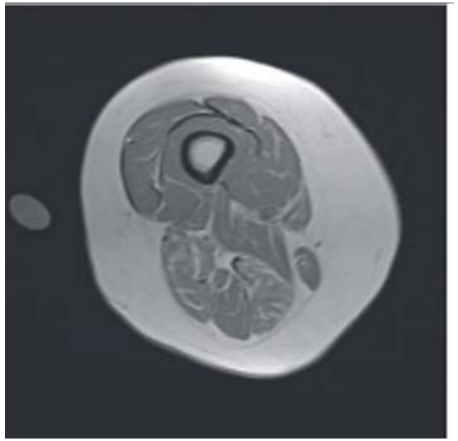
Data from SOMMA

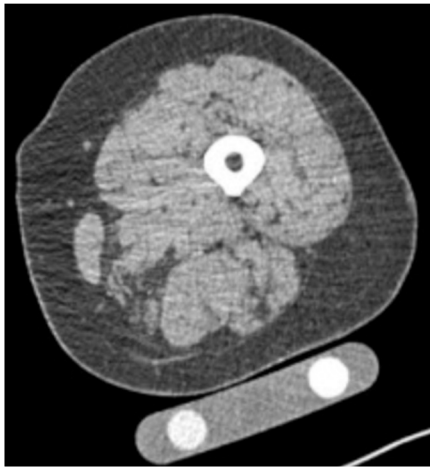
Muscle Volume

MR

CT







25 year-old woman

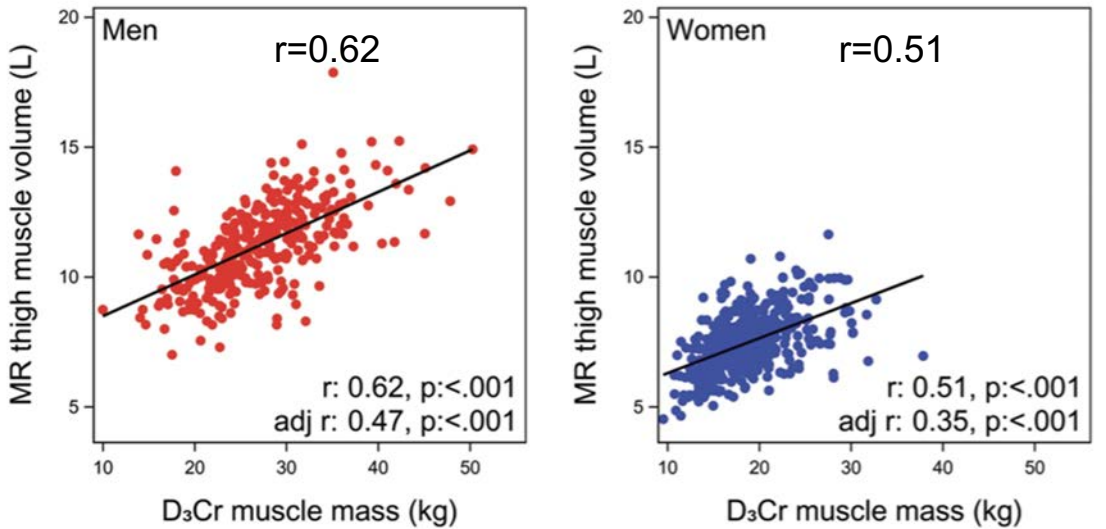
74 year-old woman

Chambers et al.J Appl Physiol 128: 368–378, 2020

Optimal vs. Acceptable Endpoint

Muscle mass by D3Cr vs. muscle volume by MR

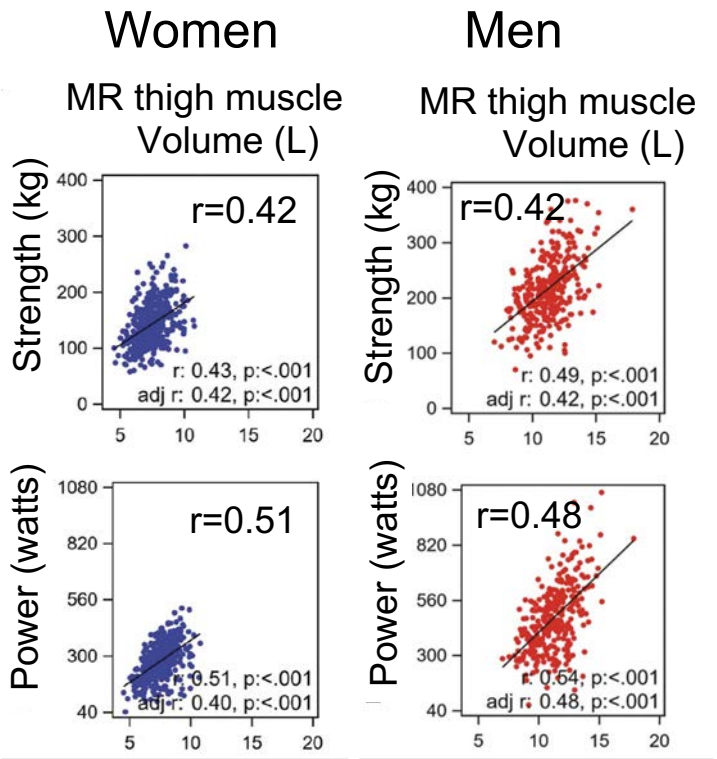
Men and women ≥ 70 years old (SOMMA Study)



Cawthon, et al. JGMS, 2024;79

MR Thigh Muscle Volume

Total thigh muscle volume is also associated with leg power and strength



Data from SOMMA

Interrelationships Between Optimal Measurements

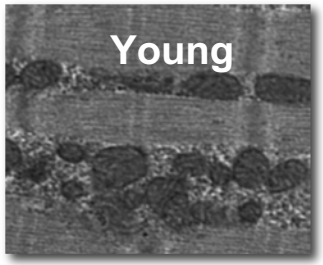
The Optimal Measurements are Moderately Correlated with Each Other

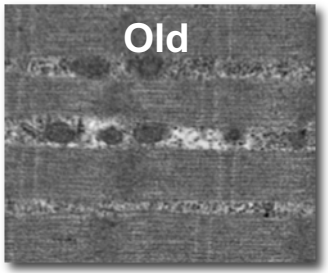
- VO_2peak and leg power — r = 0.55 (men & women)
- VO_2peak and D3Cr — r = 0.44 (men), 0.31 (women)
- Leg power and D3Cr — r = 0.44 (men), 0.30 (women)

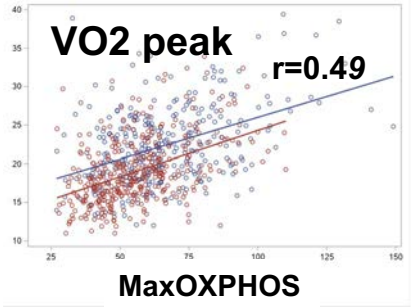
Data from SOMMA

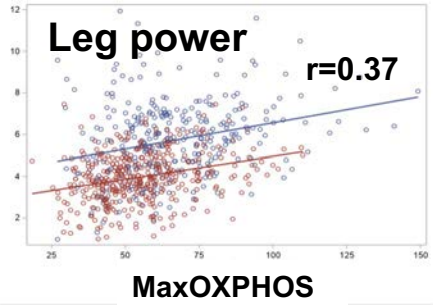
Functional Endpoints Share an Association with Mitochondrial Function in Muscle Biopsies

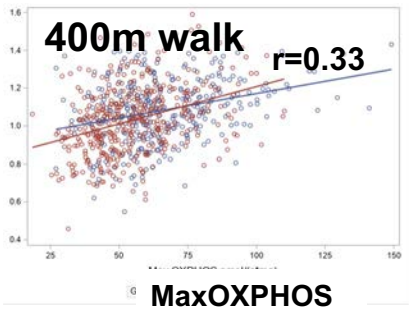
Mitochondria mass & function decline with age









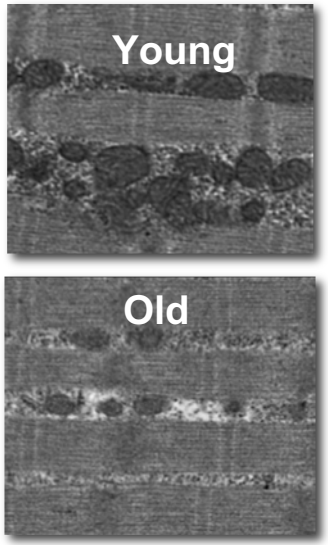


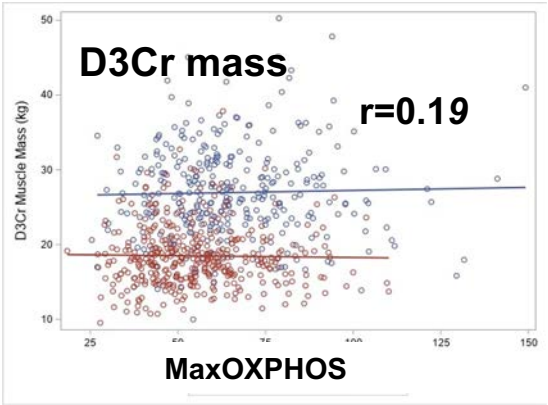
- MaxOXPHOS is a measure of maximum capacity of mitochondria to consume O2 (generate ATP)
- From muscle biopsies in the vastus lateralis in SOMMA

SOMMA data including: Mau, JGBMS 2023;78:1367–1375

However, Muscle Mass by D3Cr is Weakly Associated with Mitochondrial Function

Mitochondria mass & function decline with age





SOMMA data including: Mau, JGBMS 2023;78:1367–1375

Summary

- The muscle endpoints decline, often at increasing rate, with age
- Achieving 10-year targets may involve 10-25% improvements, depending on the measure and age
- They are moderately intercorrelated. A treatment might influence 2 or 3 in concert
- Mitochondrial function may contribute to all of the measurements except skeletal mass by D3Cr

Thank You

Peggy Cawthon
Lily Lui

Eleanor Simonsick
Luigi Ferrucci

Bill Evans
U.C. Berkeley
Duke University

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ASSESSMENT OF COGNITION

Never Stand Still | Faculty of Medicine | Centre for Healthy Brain Ageing (CHeBA)

Perminder Sachdev

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NPI Neuropsychiatric Institute

CHeBA Healthy Brains Positive Ageing

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MAIN POINTS

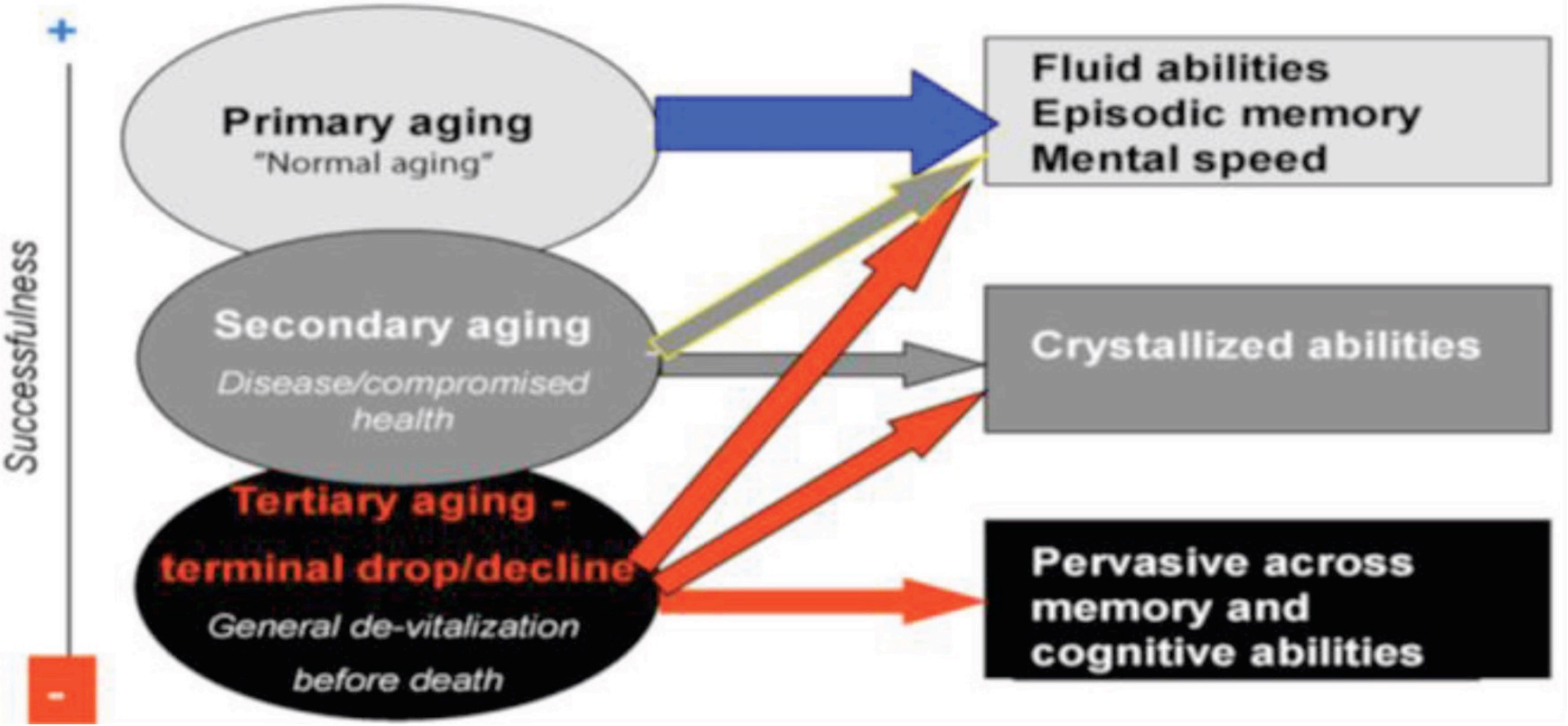
- Why cognition?
- Which aspects of cognition?
- The challenges in measuring cognition
- Suggested measures
- Addressing confounds
- Secondary markers of brain aging

UNSW THE UNIVERSITY OF NEW SOUTH WALES

MAIN POINTS

- **Why cognition?**

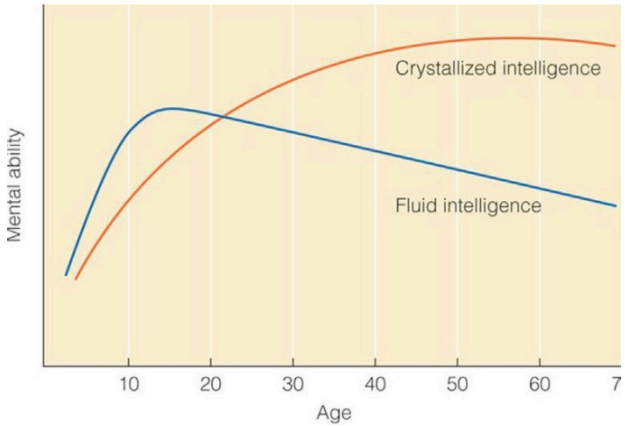
- Interest is in brain aging
  - Ageing-related changes
  - Age-related changes (pathology related)
- Functionally, most relevant (and the best studied) is age-related change in cognition.
- What is normal cognitive ageing?
  - Cross-sectional data – cohort effects
  - Longitudinal data – practice effects



Birren and Cunningham model

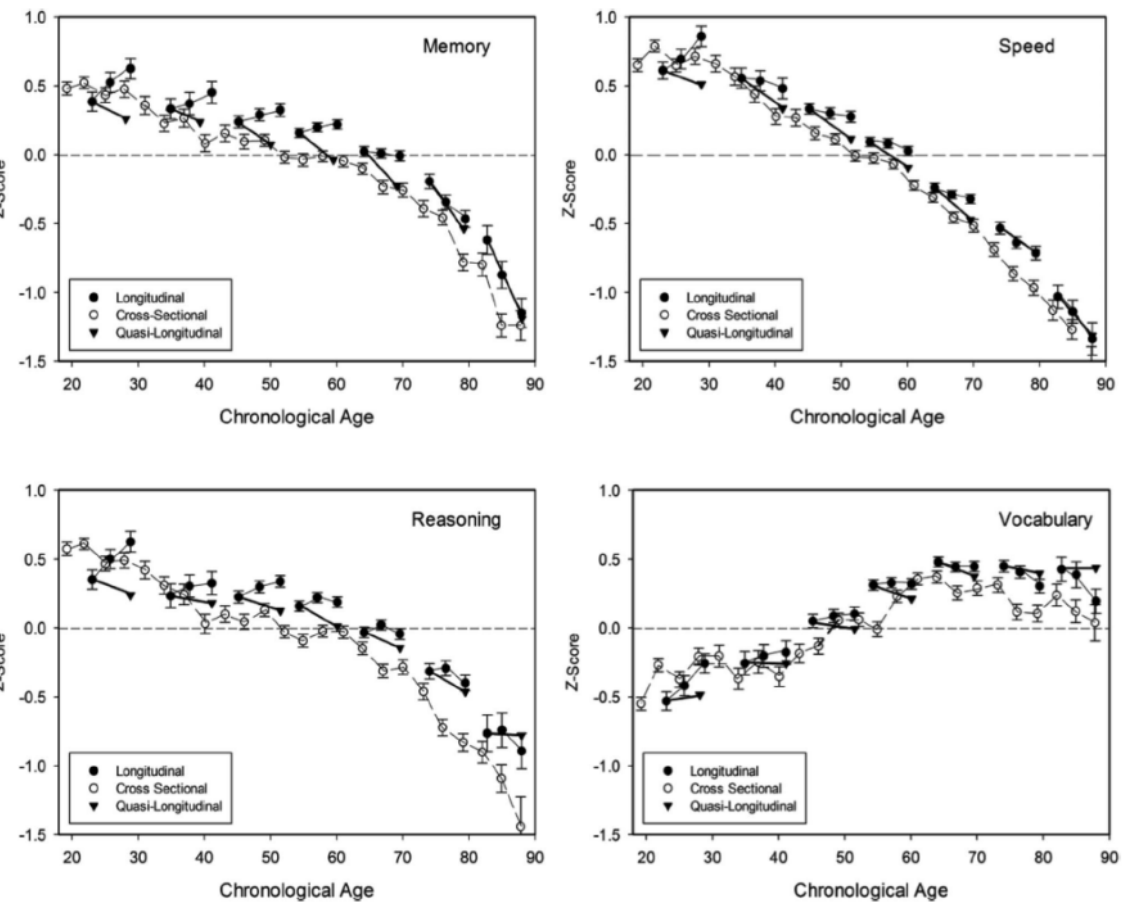
Crystallized and fluid intelligence

- **Crystallized intelligence**
  - Refers to skills, ability, and knowledge that is overlearned, well-practiced, and familiar
  - Examples: vocabulary and general knowledge
  - Crystallized abilities remain stable or gradually improve at a rate of 0.02 to 0.003 standard deviations per year through the sixth and seventh decades of life
- **Fluid intelligence**
  - Refers to abilities involving problem-solving and reasoning; includes innate ability to process and learn new information, solve problems, and attend to and manipulate one's environment.
  - Examples: executive function, processing speed, memory, and psychomotor ability.
  - Many fluid cognitive abilities, especially psychomotor ability and processing speed, peak in the third decade of life and then decline at an estimated rate of −0.02 standard deviations per year.



Cadar 2019

Harada et al, 2013



Means and standard errors of the cross-sectional and three-occasion longitudinal data and estimates of quasi-longitudinal relations in four cognitive domains.

Both cross-sectional and quasi-longitudinal comparisons indicate modest declines for memory and reasoning abilities until about age 65 when the decline accelerates, and nearly linear declines in speed from the decade of the 30's, with an increase followed by modest decline after the 60's for vocabulary.

Salthouse T, 2019

MAIN POINTS

- Why cognition?
- **Which aspects of cognition?**

Cognitive domains of interest

- Executive function
- Processing speed
- Working memory
- Psychomotor speed
- Episodic memory

Global composite

- **In order to determine if a candidate therapeutic solution is successful, the improvements must reflect percent changes in the value to offset 10-20 years decline (e.g. as if they were 10-20 younger, functionally speaking). In addition, these improvements must be individual-specific and occur across all three domains (muscle, cognitive, AND immune).**

- **A before/after design that requires that the individual changes during the treatment period**

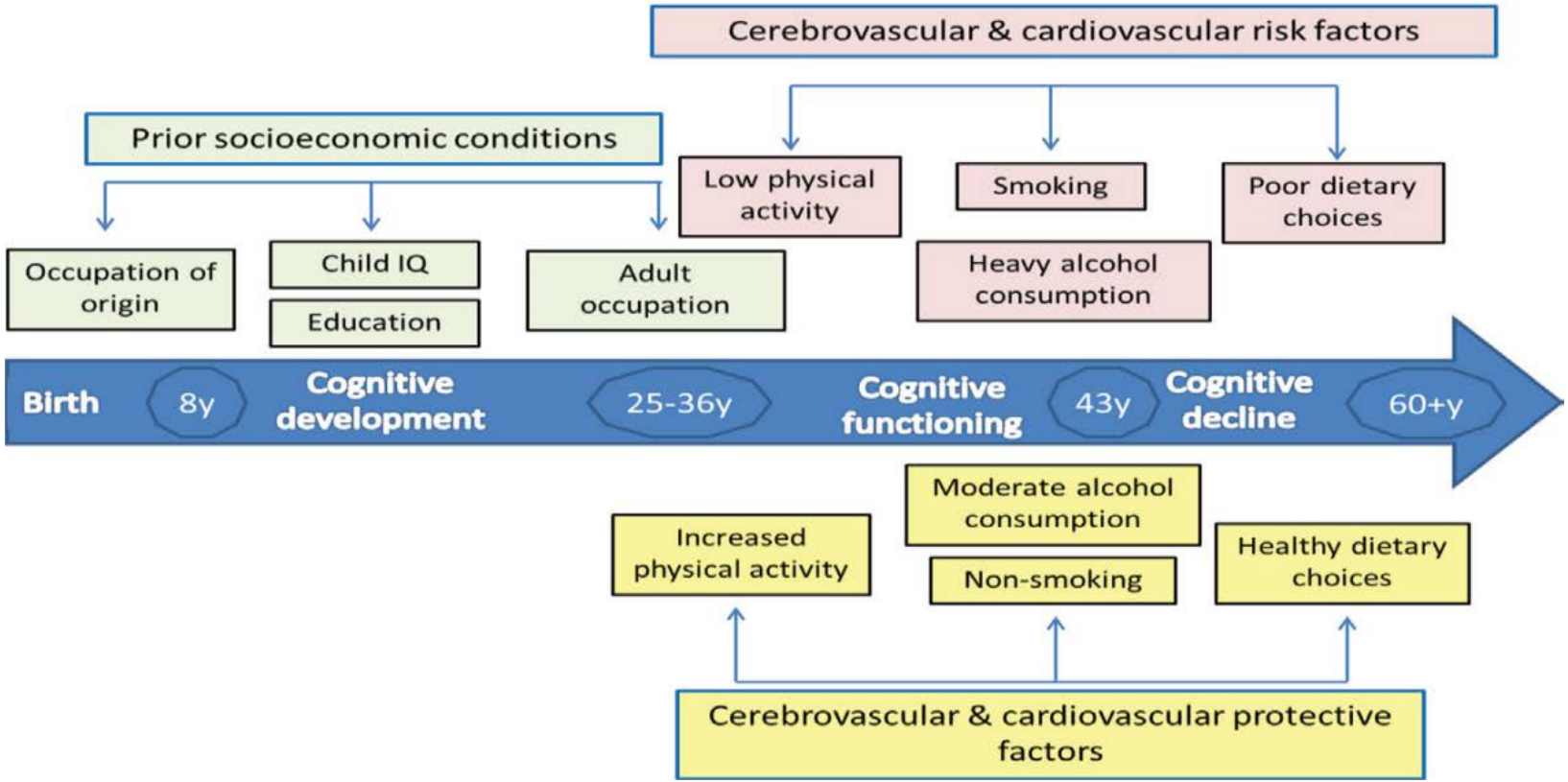
MAIN POINTS

- Why cognition?
- Which aspects of cognition?
- **The challenges in measuring cognition**

Challenges

- Demographic factors
  - Age, Sex, Education, Ethnic Background
- Language (& cultural fairness)
- Practice effects
- Normative data (its availability, and quality)
- Administration (e.g. training of staff, setting)
- Confounds (depression, poor effort, etc.)
- Confounded by type of intervention

Influencing factors across the life course



Cadar 2019

MAIN POINTS

- Why cognition?
- Which aspects of cognition?
- The challenges in measuring cognition
- **Suggested measures**

Subdomain	Type	Optimal Measure	Acceptable Measure
Cognitive Summary Score	Function	• NIH Toolbox Fluid Composite (executive function, attention and processing speed, working memory)	• CanTab / Cambridge Cognition (executive function, attention and processing speed, memory)
Recommend or Covariate • Sensory status	Function and Self-Report	• NIH Toolbox Sensory Assessments for visual acuity, pain, audition	
Recommend • Mood	Questionnaire	• NIH Toolbox Emotion assessments for sadness, psychological well-being stress and self efficacy	• CanTab / Cambridge Cognition (emotional bias test)

Cognitive Summary Score – exceed threshold for % Fluid Cognition Composite (alternative: list subcomponents separately and use the same "improvements in 2 of 3 tests" approach as muscle and immune).

CONSIDERATIONS: The therapeutic solution cannot contain an active intervention that includes activities similar to the assessment measures above. For example:

- **Team solutions cannot include practice sessions of NIH Toolbox, CanTab, or other cognitive training programs judged to be similar in scope that may permit transfer of skills.**

Measuring cognitive function

NIH TOOLBOX

https://nihtoolbox.org/domain/cognition/

- **Total Cognition Composite, Fluid Composite: includes**
  - **Dimensional Change Card Sort, (Executive)**
  - **Flanker Inhibitory Control and Attention, (Attention)**
  - **Picture Sequence Memory (Form A), (Episodic memory)**
  - **List Sorting Working Memory, and (Working memory)**
  - **Pattern Comparison Processing Speed tests (Processing speed)**

1) NIH Cognition Toolbox -Fluid composite	Good test-retest reliability & convergent validity w gold standard tests Feasible in older adults & clinical samples Available in 6 languages, measurement invariance across minority & majority ethnicities, norms available adjusted for ethnicity Assocn with biomarkers (tau, MTL vols) Preliminary support for clinical trial endpoints	Proprietary, but not very costly Small practice effects (recommend double baseline)
2) Cantab global composite	Good test-retest reliability & convergent validity with gold standard tests Feasible in older adulst & clinical samples Available in 15+ languages Language neutral as no verbal requirements, minimal association with language Assocn with biomarkers (CSF AD profile) FDA cleared as endpoint for clinical trials	Proprietary, high costs Variable findings for practice effects – moderate PEs after 3 months on subtests

Attention & processing speed	1) Symbol Digit Modalities Test	Good reliability Brief. Oral version available if motor limitations. Non-proprietary Minimal CALD effects MCIDs vs CDR-SB available Sensitive to biomarkers (incident lacunes)	Small practice effects, alternate versions available
	2) Digit Symbol Substitution - Coding	Good reliability Brief Sensitive to biomarkers (AD) FDA cleared as endpoint for clinical trials	Proprietary, costly Small practice effects
Executive function	1) TMT B	Good test-retest reliability Minimal practice effects Brief, non-proprietary High acceptance/consensus as gold standard measure of executive function MCIDs vs CDR-SB available Sensitive to biomarkers (incident lacunes)	(should administer TMT A first but very brief) CALD issues – not appropriate for character-based langua (Color Trails Test could be considered as alternative)
	2) Stroop Colour-word interference	Good test-retest reliability Minimal practice effects MCIDs vs CDR-SB availableSensitive to biomarkers (incident lacunes)	Multiple versions available – some proprietary eg D-KEFS Need to administer 2 other subtests (colour, word) to com interference score (brief tests)
Memory	1) RAVLT	Multiple measures e.g. total recall, delayed recall Good reliability for 2 sub measures above Available in multiple languages and norms well-characterised Non-proprietary Sensitive to AD biomarkers	Moderate practice effects (typical of memory measures), versions Longer duration and need to factor in the delay interval Vulnerable to CALD effects (though some measures only affected)
	2) CVLT	Multiple measures e.g. total recall, delayed recall Good reliability for 2 sub measures above	Proprietary Longer duration and need to factor in the delay interval Moderate practice effects (typical of memory measures)

MAIN POINTS

- Why cognition?
- Which aspects of cognition?
- The challenges in measuring cognition
- Suggested measures
- **Addressing confounds**

- **The NIH Toolbox Emotion** tests include four major domains: Psychological Well-Being, Stress and Self-Efficacy, Social Relationships and Negative Affect.

- **The NIH Toolbox Emotion Battery**, recommended for ages 8+, consists of tests of Positive Affect, General Life Satisfaction, Emotional Support, Friendship, Loneliness, Perceived Rejection, Perceived Hostility and Self-Efficacy. For ages 18+, the battery also includes tests of Meaning and Purpose, Instrumental Support, Sadness, Perceived Stress, Fear, and Anger.

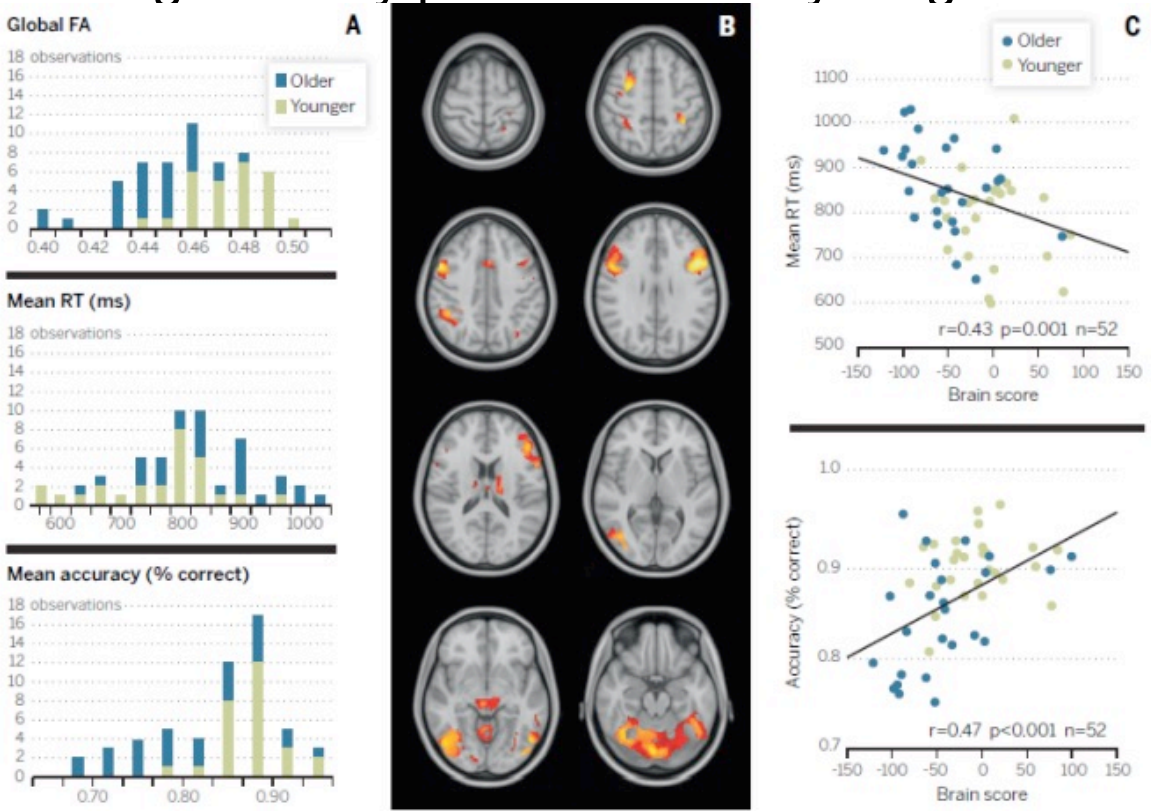
MAIN POINTS

- Why cognition?
- Which aspects of cognition?
- The challenges in measuring cognition
- Suggested measures
- Addressing confounds
- **Secondary markers of brain aging**

Neuroimaging

- Gray matter volume
- Whole brain volume
- White matter lesions
- Diffusivity measures
- Functional MRI measures
- Brain age – various measures

White matter microstructure, task-related gray matter activation, and working memory performance in young and old adults



Lindenberger, 2014

Molecular markers

- **Markers of neurodegeneration (NfL, GRAP, Tau, pTau, etc.)**
- **Markers of neuroinflammation**
- **Markers of BBB integrity, etc.**
- **Epigenetic markers (e.g., epigenetic clock)**

Conclusions

1. **Choose robust measures appropriate for the population being studied.**
2. **Measure the domains of fluid intelligence most affected by normative cognitive ageing**
3. **Address confounds**
4. **Can include secondary measures as supportive evidence**

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Immune Aging in Geroscience-Guided Trials

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UCONN
CENTER ON AGING

XPRIZE Healthspan Team Summit
11th Aging Research & Drug Discovery Meeting
Copenhagen, 8/26/2024

UConn Pepper Center
Celebrating Diversity and Heterogeneity in Aging

Disclosures

- Funding from NIH (NIA, NIAID, NINR, NCI, Common Fund) and PCORI
- Voting member of ACIP (Advisory Committee on Immunization Practices) at CDC
- **No** relevant commercial disclosures

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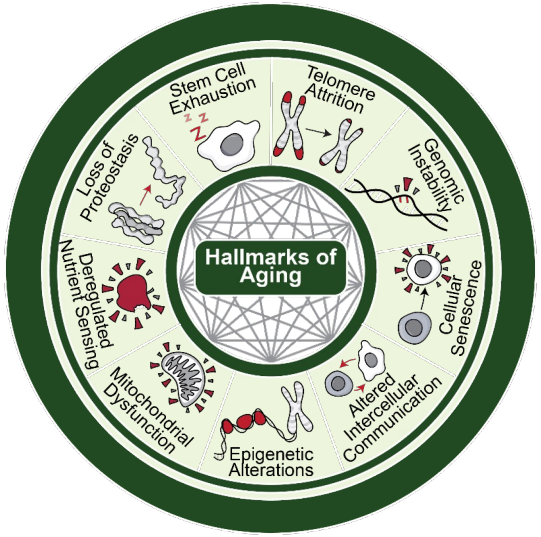
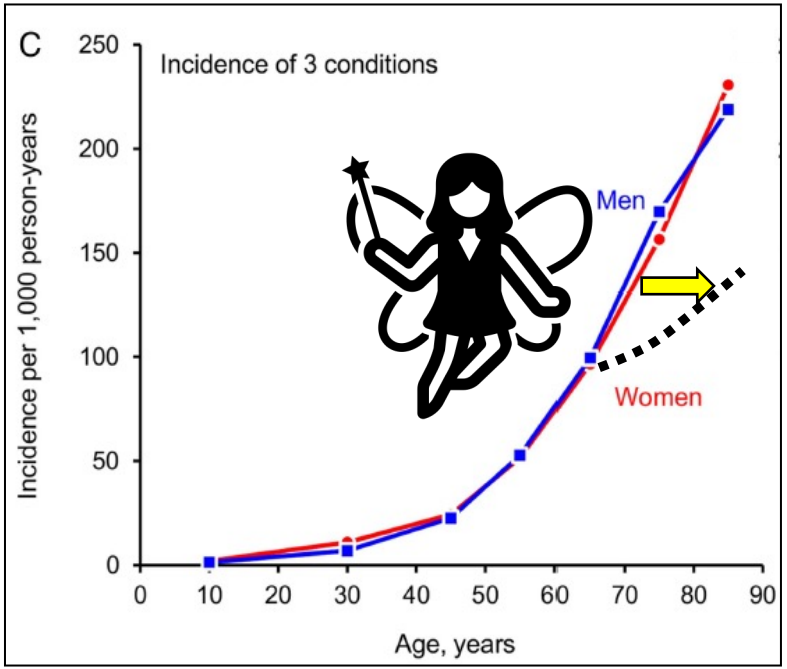
Moving Gerotherapeutics from an Idea to Reality





St Sauver JL *et al. BMJ Open 2015*

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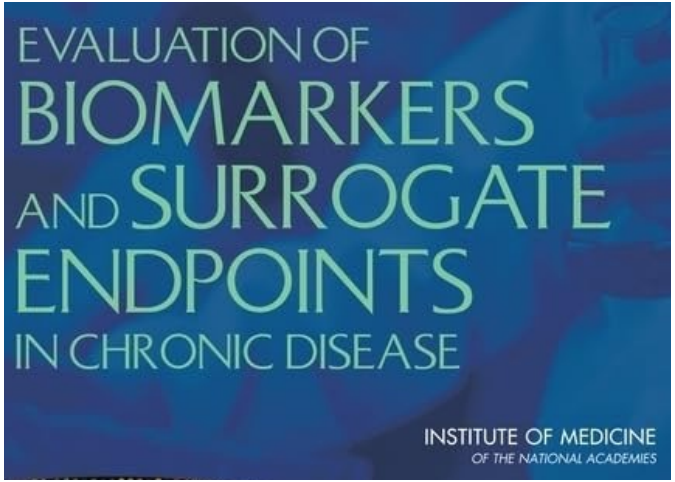
Traditional View of Disease Biomarkers



Biomarker

A characteristic (e.g. cholesterol level) that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to an intervention (2010).

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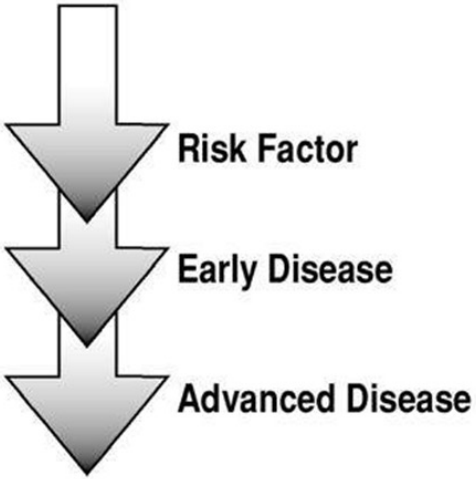
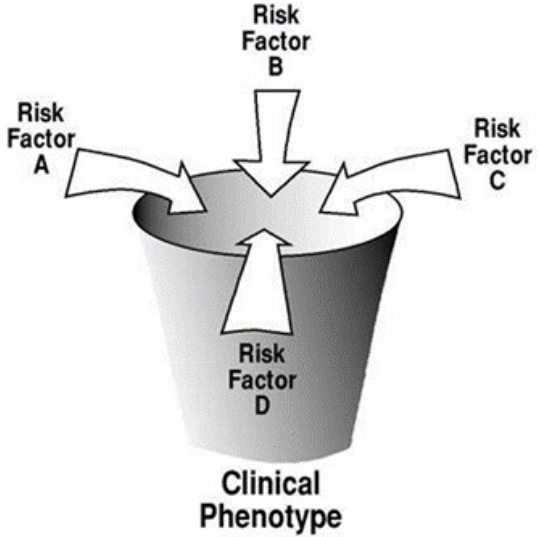
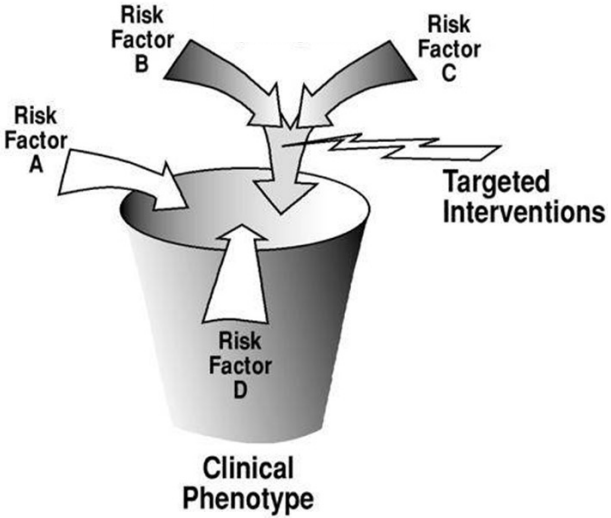
Biomarkers and Multifactorial Complexity of Aging







Geriatric syndromes: clinical, research, and policy implications of a core geriatric concept
Inouye SK, Studenski S, Tinetti ME, and Kuchel GA. *JAGS*. 2007

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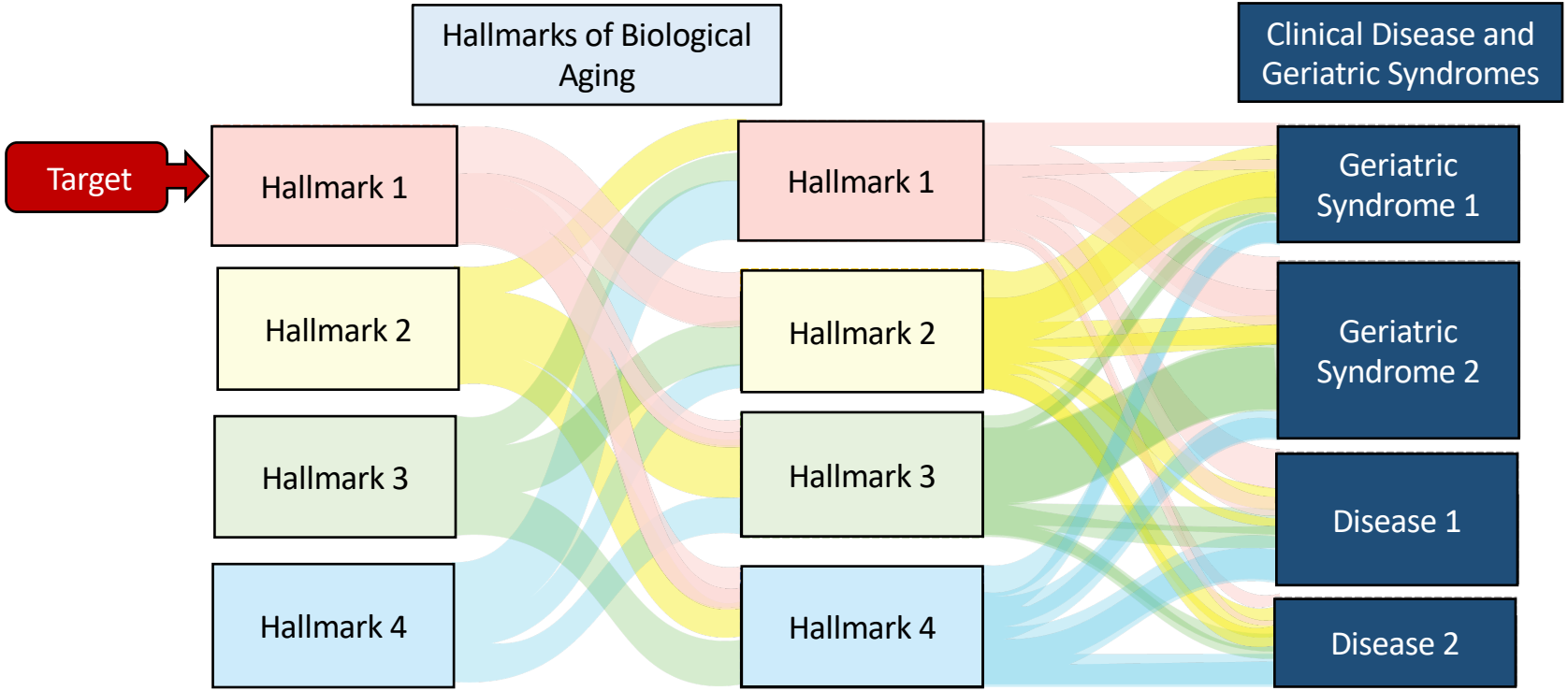
Biomarkers and Multifactorial Complexity of Aging



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Espinoza, Justice, Newman, Pignolo and Kuchel;
Chapter 40 Applied Clinical Geroscience,
Hazzard's Geriatric Medicine and Gerontology, 8th edition

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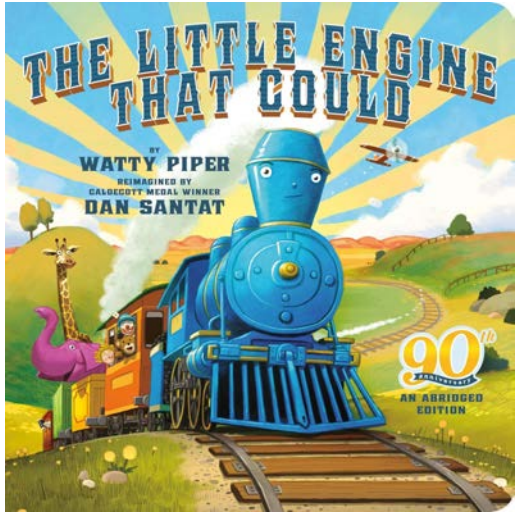
Celebrating Diversity and Heterogeneity in Aging

Biomarkers for Geroscience-Guided Clinical Trials



Targeting Aging with Metformin (TAME) study design overview

Age 65-80 AND Gait speed 0.4-1.0 m/sec OR Age-related disease (CVD, cancer, MCI)	Inclusion Criteria
n = 3000 **Double blind placebo-controlled trial**	
(Clinical) Time to incidence of any major age-related disease: **MI, stroke, cancer, CHF, MCI/dementia, or death.**	Primary Outcome
(Functional) Time to incidence of disability: Major decline in mobility or cognitive function, onset of severe ADL limitation.	Secondary Outcome
(Biological) Change in metformin levels and biomarkers of aging and age-related diseases.	Tertiary Outcomes

GeroScience (2018) 40:419–436
https://doi.org/10.1007/s11357-018-0042-y

REVIEW ARTICLE

A framework for selection of blood-based biomarkers for geroscience-guided clinical trials: report from the TAME Biomarkers Workgroup

Jamie N. Justice · Luigi Ferrucci · Anne B. Newman · Vanita R. Aroda · Judy L. Bahnson · Jasmin Divers · Mark A. Espeland · Santica Marcovina · Michael N. Pollak · Stephen B. Kritchevsky · Nir Barzilai · George A. Kuchel

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Role of Immune Aging within XPRIZE Competition

Immune Function Outcomes: Improvement from baseline that exceeds personalized response thresholds in 2 out of 3 biospecimen-based biomarker categories as measured by central XPRIZE laboratories.

Specific assay decisions will be determined in 2026, but may include:

- cytokine/multikine assays
- immune cell composition (e.g. IMM-AGE)
- *ex vivo* naïve immune response to a new stimulus

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Circulating Humoral Biomarkers for Geroscience-Guided Clinical Trials

Biomarker	Underlying Biologic Process & Role
IL-6, CRP TNFRII	**Inflammation & Intercellular Signaling** Interleukin 6 (IL-6) is a proinflammatory cytokine and Tumor Necrosis Factor-α RII Is a TNF -α receptor involved in acute-phase response. C-Reactive Protein (CRP) is an acute phase protein produced in response to inflammation. Cytokine dysregulation is a driver of pathophysiologic processes leading to disease, functional decline, frailty, and death.
GDF15	**Stress Response & Mitochondria** Growth Differentiating Factor 15 (GDF15) is a member of the TGF-β superfamily robustly associated with mortality, cardiovascular events, cognitive decline and dementia. GDF15 is increasingly recognized in mitochondrial dysfunction, and as a biomarker of aging.
IGF-1 Insulin	**Nutrient Signaling** Disruption of the insulin/ insulin-like growth factor (IGF-1) signaling pathway is implicated in longevity in animal models. In humans, IGF-1 and fasting insulin are responsive to caloric restriction, and low IGF-1 in growth hormone receptor deficiency conveys disease protection.
Cystatin-C	**Kidney Aging** Cystatin C, an extracellular inhibitor of cysteine proteases, is a marker of renal disease and aging. It is an independent risk factor for all cause and CVD-related mortality, and multi-morbidity, and higher levels are consistently associated with poor physical function and cognition.
NT-proBNP	**Cardiovascular Health** B-type natriuretic peptides (BNP, NT-proBNP) are secreted in response to cardiomyocyte stretching to decrease vascular resistance. NT-proBNP has a greater-half life and accuracy compared with BNP and is used to diagnose and establish prognosis for heart failure.
HGBA1c	**Metabolic Aging** Glycated hemoglobin (hemoglobin A1c, HGBA1c) is formed in a non-enzymatic glycation pathway and is a marker for 3-mo average plasma glucose. High HGBA1c reflects poor glucose control, and in older nondiabetics is strongly associated with death, chronic disease, and functional decline.
Molecular Signature	**Epigenetic, Interdependent, Multi-Omic** Data intensive molecular platforms can explore global changes in epigenetic, transcriptomic, proteomic and proteostasis, and small metabolite signatures. These approaches may better capture complex and multifactorial processes underlying aging.

Criteria for Selection:

1. **Measurement reliability and feasibility**
2. **Relevance to aging**
3. **Robust and consistent ability to predict all-cause mortality, clinical and functional outcomes**
4. **Responsiveness to intervention being tested**

GeroScience (2018) 40:419–436
https://doi.org/10.1007/s11357-018-0042-y

REVIEW ARTICLE

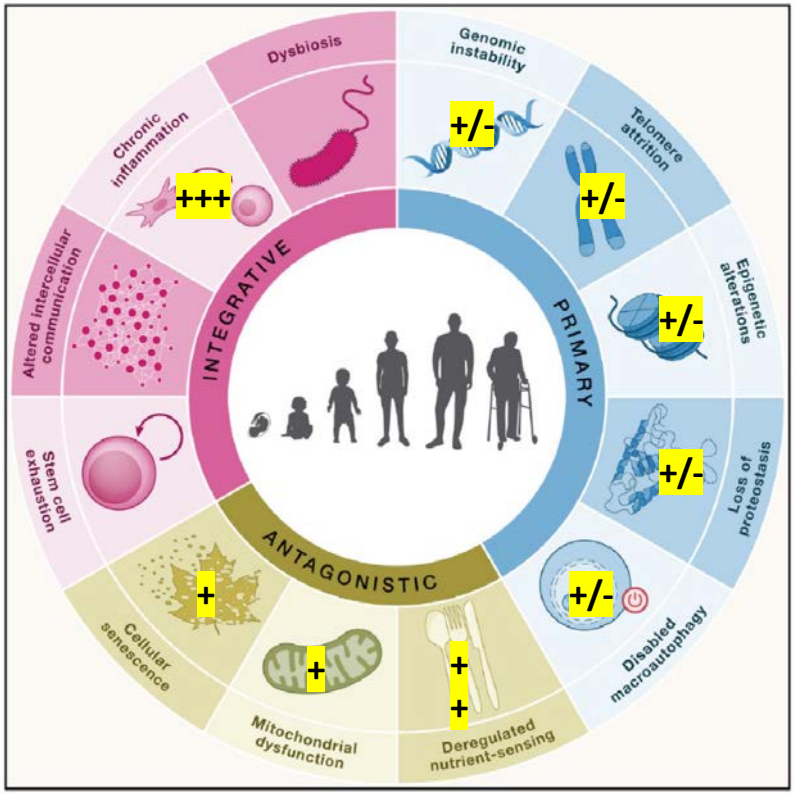
A framework for selection of blood-based biomarkers for geroscience-guided clinical trials: report from the TAME Biomarkers Workgroup

Jamie N. Justice · Luigi Ferrucci · Anne B. Newman · Vanita R. Aroda · Judy L. Bahnson · Jasmin Divers · Mark A. Espeland · Santica Marcovina · Michael N. Pollak · Stephen B. Kritchevsky · Nir Barzilai · George A. Kuchel

UCONN CENTER ON AGING

UConn Pepper Center
Celebrating Diversity and Heterogeneity in Aging

Need to Study Immune Aging in Cells



+ Ability to obtain measurements using <u>serum</u> or <u>plasma</u> that can provide insights into underlying biology of aging

Lopez-Otin et al. *Cell* 2023

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Need to Study Immune Resilience

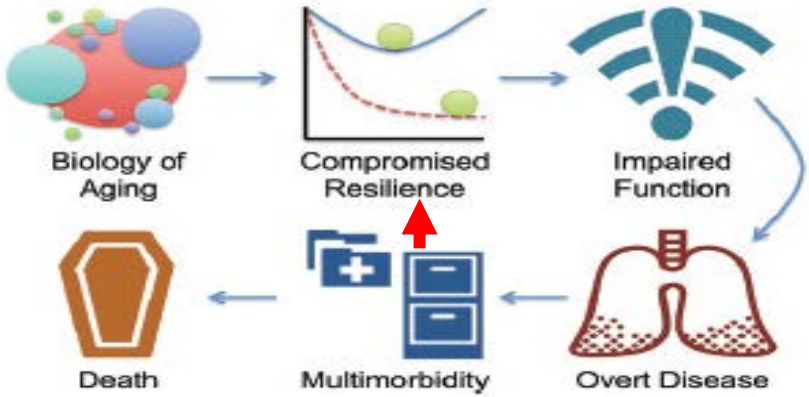
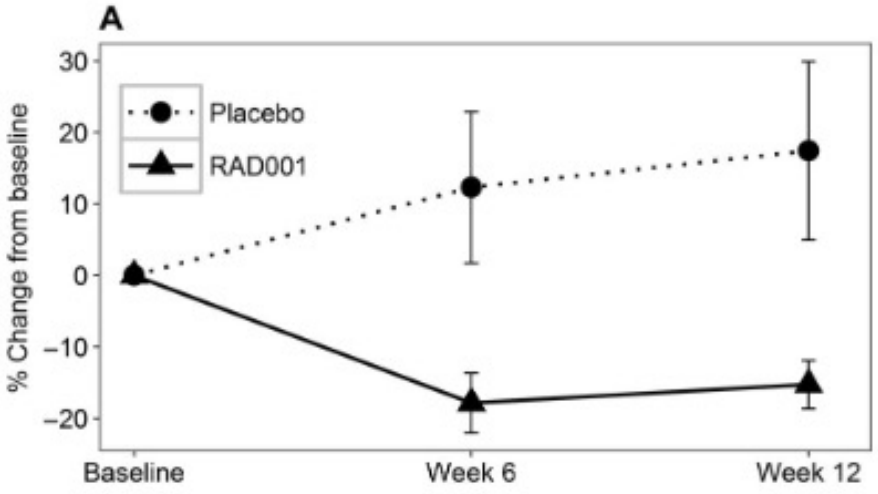


Figure 1. Aging, physical resilience, health span and life span. The geroscience hypothesis posits that the fundamental biology of aging ultimately drives chronic disease, multimorbidity, and death. Robust resilience to a health stressor in early-to-mid-life (solid line) may be indicative of healthy aging. In contrast, compromised resilience (dashed line) may signal advanced aging, before the emergence of static signals of organ or physiological dysfunction. Early-to-midlife resilience may be predictive of health span and life span.



Decreased PD1-positive CD4+ T cells in mTOR inhibition

mTOR inhibition improves immune function in the elderly

Joan B. Mannick,[1]* Giuseppe Del Giudice,[2] Maria Lattanzi,[2] Nicholas M. Valiante,[3] Jens Praestgaard,[4] Baisong Huang,[1] Michael A. Lonetto,[1] Holden T. Maecker,[5] John Kovarik,[6] Simon Carson,[7] David J. Glass,[1] Lloyd B. Klickstein[1]

Science Translational Med. 2014

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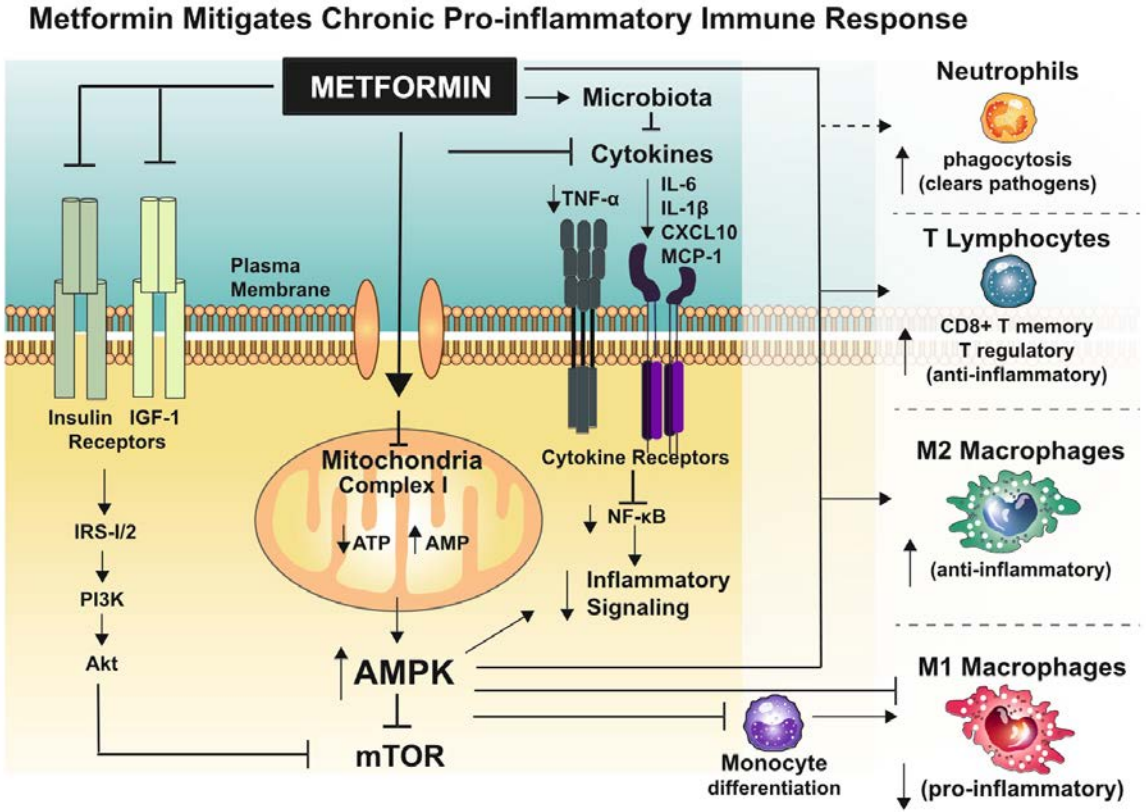
Vaccination Efficacy With Metformin in Older Adults (VEME)

Jenna Bartley, PhD
Assistant Professor,
UConn Center on Aging,
Department of Immunology
UConn Pepper Scholar

Justice *et al. Geroscience* 2021



afar american federation for aging research

TRANSLATIONAL GEROSCIENCE NETWORK

UCONN CENTER ON AGING

UConn Pepper Center
Celebrating Diversity and Heterogeneity in Aging

Heterogeneity of Immune Resilience

nature immunology

Article

https://doi.org/10.1038/s41590-023-01717-5

Distinct baseline immune characteristics associated with responses to conjugated and unconjugated pneumococcal polysaccharide vaccines in older adults

Received: 21 April 2023

Accepted: 21 November 2023

Published online: 5 January 2024

Check for updates

Sathyabaarathi Ravichandran[1,11], Fernando Erra-Diaz[1,8,11], Onur E. Karakaslar[1,9,11], Radu Marches[1], Lisa Kenyon-Pesce[2], Robert Rossi[1], Damien Chaussabel[1], Djamel Nehar-Belaid[1], David C. LaFon[3], Virginia Pascual[4], Karolina Palucka[1], Silke Paust[1,5], Moon H. Nahm[3], George A. Kuchel[2], Jacques Banchereau[1,10] & Duygu Ucar[1,6,7]

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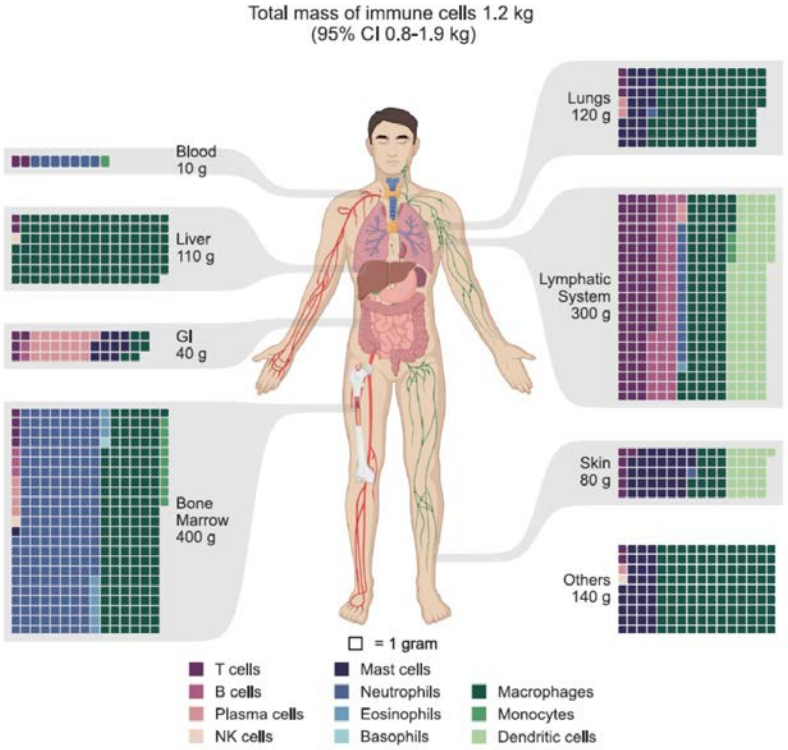
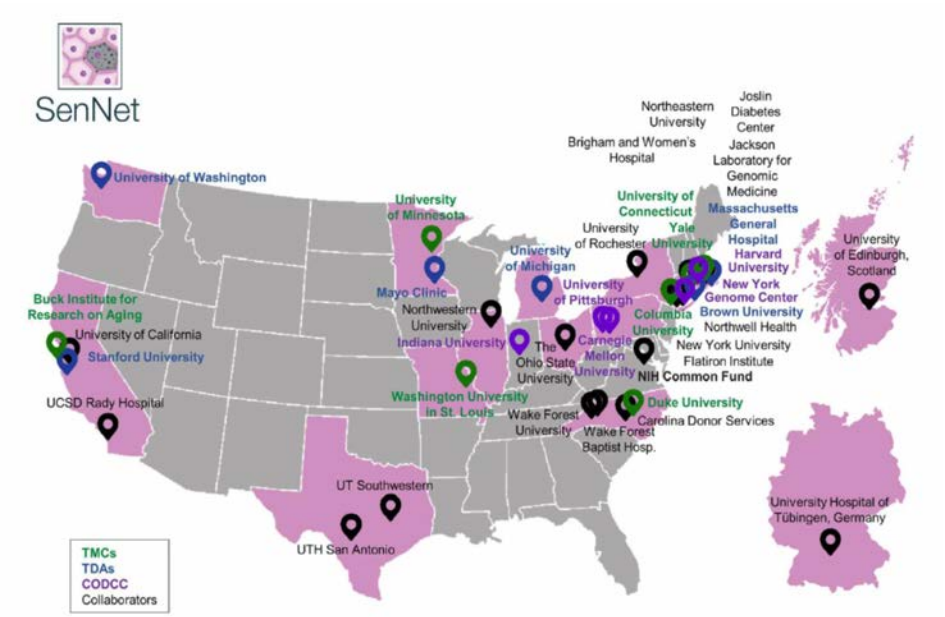
Limitations, Challenges and Opportunities



Sender *et al. PNAS* 2023



Lee *et al. Nature Aging* 2022

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Conclusions

- Measures of immune aging may help guide gerotherapeutic trials
- Humoral (serum- or plasma-derived) biomarkers are easiest and best validated, yet they offer more limited biological information
- Cell-based immune measures and potential for deeper biological insights
- Moving beyond the “baseline” and importance of addressing resilience
- Remarkable multidimensional heterogeneity
- Don’t let the perfect become the enemy of the good!

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XPRIZE HEALTHSPAN | HEVOLUTION | SOLVE FSHD

03

PANEL DISCUSSION
REGULATORY, ETHICS, AND SAFETY

REGULATORY, ETHICS, AND SAFETY

LAURA GOETZ, MD
XPRIZE Healthspan

ALEXANDER "ZAN" FLEMING, MD
Kinexum

BART VAN DER SCHUEREN, MD, PHD
University of Leuven

ALBERTO APARICIO, PHD
University of Texas Medical Branch

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04

INVESTOR'S SESSION

INVESTOR'S SESSION

YIANNI PSALTIS, PHD
Exponential Ventures

ALEX COLVILLE
age1

MARC BERNEGGER
Maximon

LADA NUZHNA
Impetus Grants

XPRIZE HEALTHSPAN | HEVOLUTION | SOLVE FSHD

05

WHAT'S NEXT

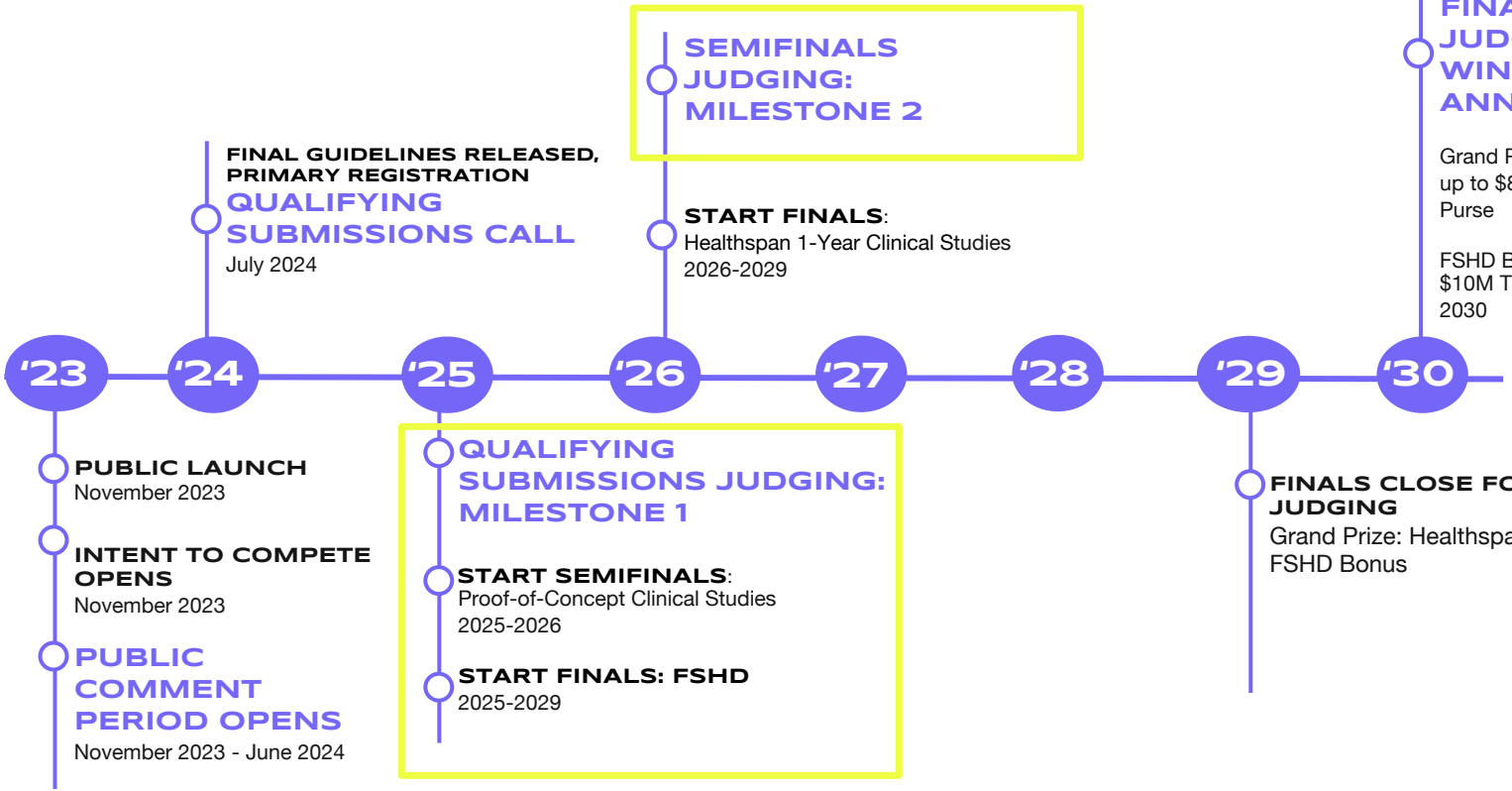
WHAT'S NEXT

LAUREN PIERPOINT, PHD
XPRIZE Healthspan

BRIANNA STUBBS, PHD
Buck Institute on Aging

KEY MILESTONES

KEY MILESTONES



+ Annual Team Summits Years 1-7 and Biomarker Summits Years 1-3
+ Town Halls, Alumni Network and Partnership Activities

QUALIFYING SUBMISSIONS

QUALIFYING SUBMISSION

PURPOSE: first formal opportunity for teams to demonstrate their ability to compete in the $101M Healthspan competition and $10M FSHD Bonus Prize

DUE 20 DECEMBER 2024!

QUALIFYING SUBMISSION

Research
& Development

Milestone 1:

- $10M
- $2M FSHD

Approximately 12 pages

- Summary……1pg
- Team……2pg
- Environment and Clinical Centers……. 2pg
- Technical Application……5pg
- Study Timeline…….. 1pg
- Scalability / Accessibility…….. 1pg

\+ Human Subjects Safety, Resourcing Plan, Biohazard

QUALIFYING SUBMISSION

QUALIFYING SUBMISSION

Research
& Development

Milestone 1:

- $10M
- $2M FSHD

RESEARCH TYPES: What types of preliminary evidence can be submitted?

- Secondary research
- Preclinical studies in animals
- Clinical observations in patient populations
- *In silico* research

QUALIFYING SUBMISSION

TEAMS MUST SUBMIT A QUALIFYING APPLICATION FOR XPRIZE HEALTHSPAN AND FSHD BONUS PRIZE

QUALIFYING SUBMISSION

Research
& Development

Milestone 1:

- $10M
- $2M FSHD

Qualifying Submission	XPRIZE Administrative Review	XPRIZE Judges Review	Milestone 1 Award Ceremony
20 December, 2024	January 2025	March 2025	2nd Quarter 2025 (exact dates pending)

QUALIFYING SUBMISSION

QUALIFYING SUBMISSION

Research
& Development

Milestone 1:

- $10M
- $2M FSHD

JUDGING QS / MILESTONE 1

Judges will evaluate:

- Team
- Environment & Clinical Center(s)
- Scientific Rationale & Preliminary Data
- Approach to Semi-Finals Testing
  - Study Design
  - Ethical Issues
  - Data Management & Statistical Analyses
  - Sample Size Justification
- Study Timeline
- Scale & Accessibility

TESTING & JUDGING

QUALIFYING SUBMISSION

Research
& Development

Milestone 1:

- $10M
- $2M FSHD

40 TEAMS

SEMI-FINALS

Proof-of- Concept
Clinical Studies

Milestone 2:

- $10M

10 TEAMS

FINALS

1-year Clinical Trials in
Older Adults

Grand Prize:

- $81M
- $8M FSHD

8 FSHD TEAMS ADVANCE TO FINALS

SEMIFINALS TESTING

SEMI-FINALS TESTING

SEMI-FINALS

Proof-of- Concept Clinical Studies

Milestone 2:

- $10M

EARLY STAGE / PROOF-OF-CONCEPT CLINICAL STUDIES

Typically short (less than 30-60 days), small (5-20 people receive active intervention), and relatively inexpensive studies that are used to help design and justify larger clinical trials

For XPRIZE Healthspan Semi-Finals, these trials are used to indicate **readiness** for Finals and **feasibility** of approach

SEMI-FINALS TESTING

PURPOSE: Early-stage/proof-of-concept trials

- Show feasibility of approach
- Engage clinical center
- Refine recruitment
- Develop study methods
- Evaluate dosing, formulation, route of administration
- Regulatory approvals
- Demonstrate safety
- Generate supporting data for future Finals clinical trials
- Go/No-Go

SEMI-FINALS TESTING & JUDGING

SEMI-FINALS

Proof-of- Concept Clinical Studies

Milestone 2:

- $10M

EARLY STAGE / PROOF-OF-CONCEPT CLINICAL STUDIES

April 2026: Data Submission & Finals Application

At the end of Semi-Finals, teams will submit:

1. Recruitment / enrollment reports
2. Analyses and data reports
3. De-identified data set
4. Finals application

SEMI-FINALS TESTING & JUDGING

SEMI-FINALS

Proof-of- Concept Clinical Studies

Milestone 2:

- $10M

JUDGING SEMI-FINALS / MILESTONE 2

Judges will evaluate:

- Team and clinical center readiness
- Regulatory approvals
- Recruitment reports
- Ability to collect, manage, and submit data
- Preliminary data & Semi-Finals study reports
- Adherence to timeline
- Initial estimates of safety and human subjects protections

TESTING & JUDGING

QUALIFYING SUBMISSION

Research
& Development

Milestone 1:

- $10M
- $2M FSHD

40 TEAMS

SEMI-FINALS

Proof-of- Concept
Clinical Studies

Milestone 2:

- $10M

10 TEAMS

FINALS

1-year Clinical Trials in
Older Adults

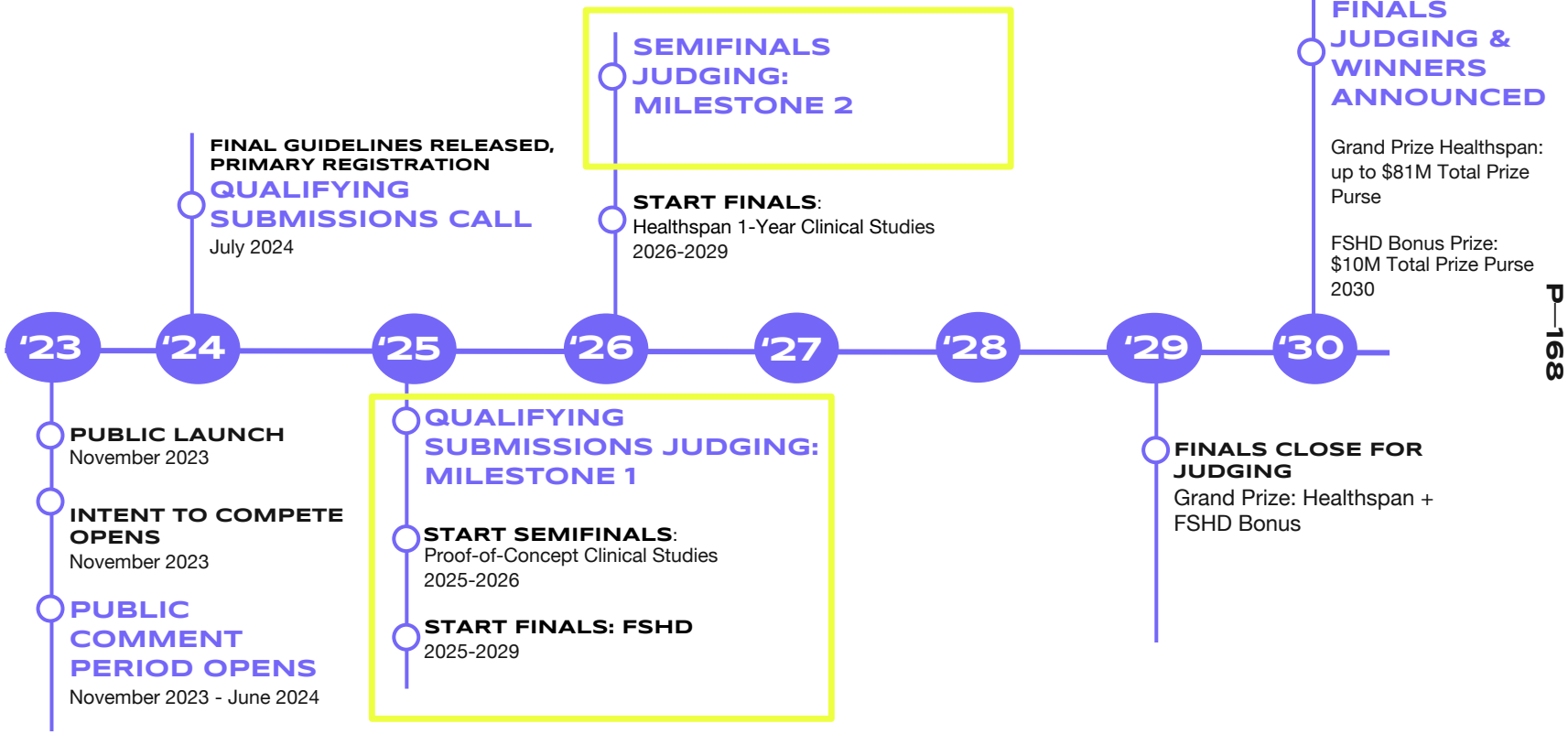
Grand Prize:

- $81M
- $8M FSHD

8 FSHD TEAMS ADVANCE TO FINALS

NEXT STEPS

KEY MILESTONES



+ Annual Team Summits Years 1-7 and Biomarker Summits Years 1-3
+ Town Halls, Alumni Network and Partnership Activities

INTERESTED IN PARTICIPATING?

VISIT XPRIZE.ORG/HEALTHSPAN

ENGAGE WITH US AS A TEAM

EMAIL

Healthspan@xprize.org

SLACK

Pre-registered teams can join our community

OFFICE HOURS

Host bi-weekly for pre-registered teams

CONNECT

Find partners and resources

WORKSHOP

Learn about all things Healthspan

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Case Study Insights:
Clinical Study Design for XPRIZE Healthspan

XPRIZE Healthspan Team Summit
Monday 26th August 2024
Brianna Stubbs, PhD & John Newman MD, PhD
Buck Institute for Research on Aging
Novato, California USA

Buck

Disclosures
HVMN Inc: stock
BHB Therapeutics, Ltd: stock options
Selah Therapeutics, Ltd: Co-founder, stock options

Live better longer.

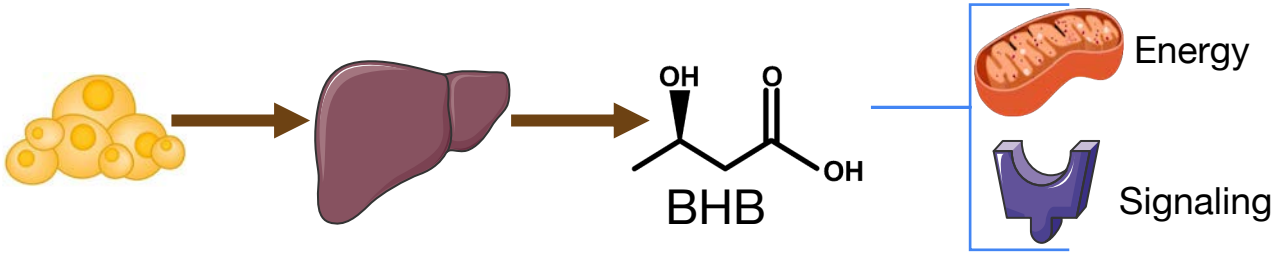
Considerations for Pilot Geroscience Clinical Trials

- Feasibility of recruitment and endpoints at your site
- Demonstrate safety, tolerance and feasibility in older adult population
- Identify differences in PK or PD in older adults
- Population selection
- Endpoint selection – clinically meaningful functional outcomes and biomarkers linked to aging

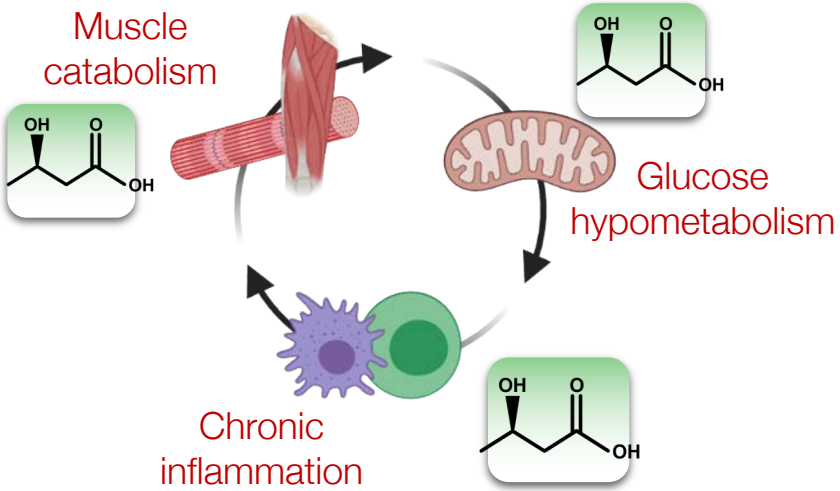
Case study: pilot study of ketone esters – 2022-23 enrollment

Buck

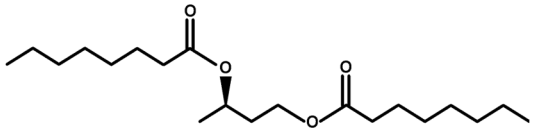
Long-Term Goal: Test Ketones in Frailty Without Diet Changes



Frailty



Ketone Ester



Pilot needed to fill key gaps…

- Safety: longest study 28 days
- Safety, tolerance and feasibility: No study in older adults
- Mechanistic clues: No study of aging biology

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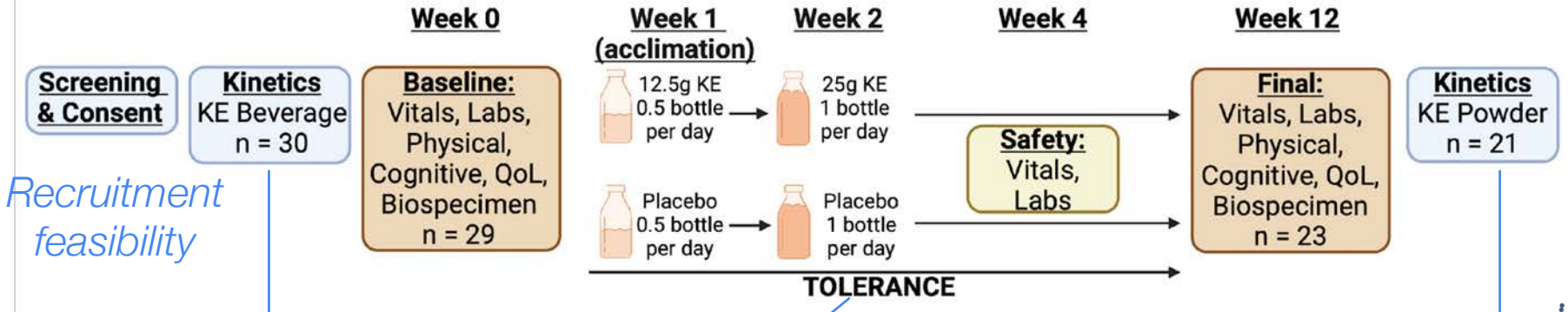
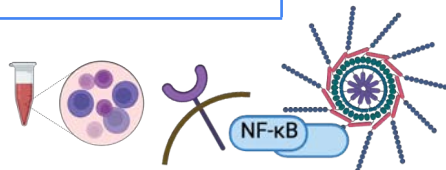
Geroscience Proof of Concept, Pilot Study of Ketone Ester

Randomized, double-blind, placebo-controlled pilot trial of n = 30 healthy older adults



Recruitment feasibility



Confirm kinetics in the target (older) population

Specifically test safety and tolerability* in target population *+retention*

Look for a signal in clinically meaningful, standardized outcomes *+ endpoint feasibility*

Mechanistic biomarker outcomes

* Primary outcome

NCT05585762

Buck

Pilot Demonstrated Safety and Tolerance in Older Adults

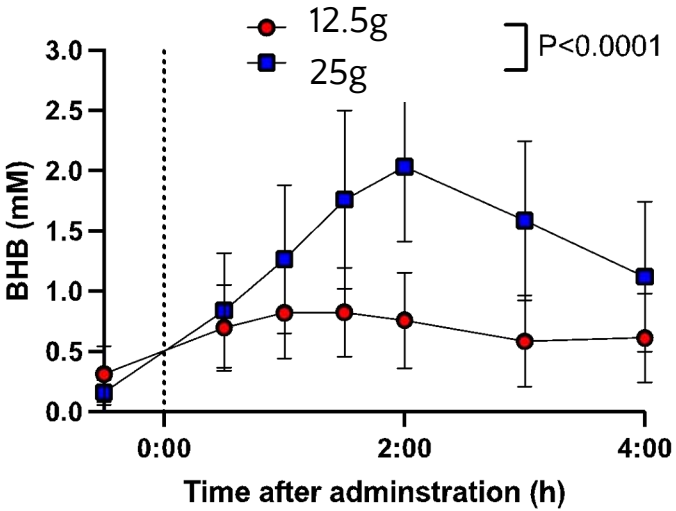
- **Successfully enrolled n = 30 subjects within ~6 months**
  - 1:1 male: female ratio. Median age = 75.8 (65 – 89)y. 90% white.
- **Primary outcome:** "Proportion of subjects with moderate-severe dizziness, headache or nausea >1 day after 2 weeks of dose escalation (week 3 onward)"
  - PLA = 1/14 *(one subject dropped out within 2 weeks)*
  - KE = 2/14 *(all subjects completed at least 3 weeks)*
- **Total side effects were low and not different KE vs Placebo**
- **No serious adverse events**
- **6 subjects did not complete:**
  - **KE= 2/14** [1 = GI issues, 2 = GI issues, h/o pancreatitis (PI withdrew)]
  - **Placebo = 4/15** [1 = Pre-existing cholesterol trend (PI withdrew), 2 = Low energy, 3 = GI issues, 4 = Tiredness and low mood]
- **No changes in key safety labs:** lipids, liver function, acid:base balance
- **No changes in vital signs:** weight, heart rate, blood pressure seated and standing)

Stubbs et al 2024, JNHA

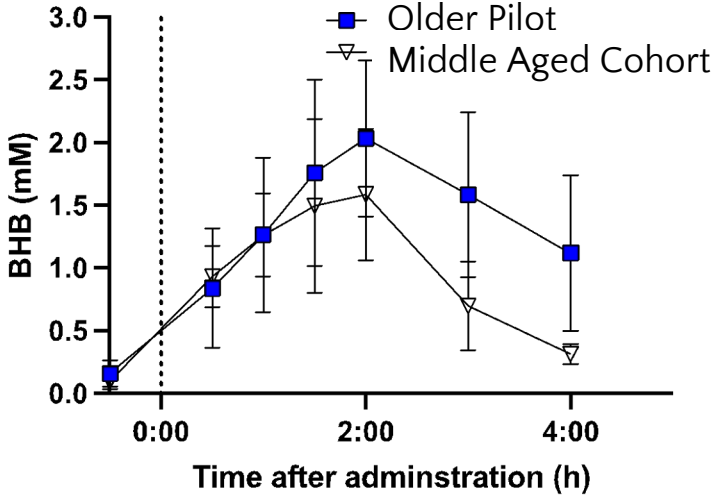
Buck

Pilot illustrated older adult specific PK

Pilot Study BHB PK Data



Pilot vs Middle Aged Cohort



Pre-print of PK data

Older Adult Pilot: Median Age **76** (65-89)
Middle Age: Median Age **51** (30-65)

Middle aged cohort: Stubbs et al., Toxicol Res Appl 2023
https://doi.org/10.1177/23978473231197835

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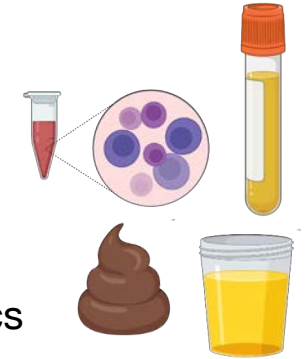
Pilot Secondary and Exploratory Analyses Ongoing

Chronic inflammation and senescence:

- Immunophenotyping
- MS Proteomics (SASP)*
- Cytokines
- Microbiome*



Energetics:

- PBMC bioenergetics
- GC/MS Metabolomics
- NMR, GC/MC Lipidomics

Aging biomarkers:

- Belsky BioAge
- DNAm epigenetic clocks
- TAME consortium biomarkers

***Signal of target engagement in early data**

No signal in physical, cognitive or quality of life outcomes

- Small sample size
- Healthy population
- Limited duration

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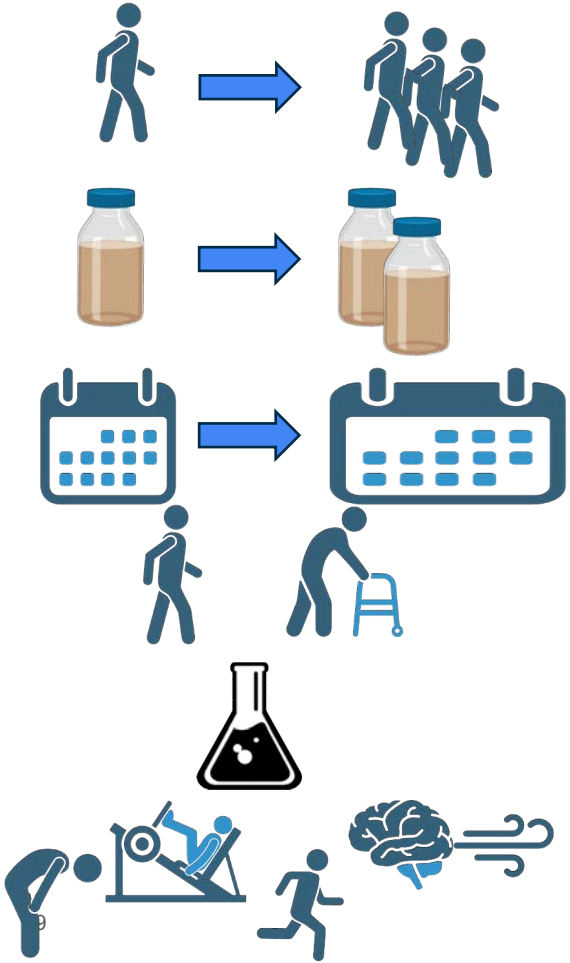
Changes from Pilot to Follow-Up



Expanded sample size – multisite*
** Addition of a coordinating center*
Increased diversity

Daily to BID dosing (25g)
Favorable tolerability and safety

12 weeks to 20 weeks
Favorable adherence, no dropout after 4 weeks

Gait speed inclusion criteria 0.6-1.0 m/s
13/29 pilot participants

Additional mechanistic insights
Muscle biopsy, deep immune phenotyping

Composite vigor-frailty outcome
Capture key elements of the frailty syndrome

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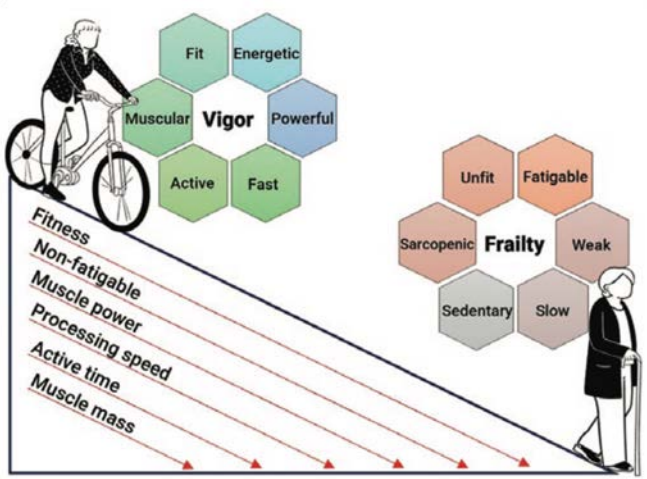
Composite Primary Outcome for Follow-Up Pre-Frail Study

Fried Frailty Phenotype

- 1RM leg press strength — **Weakness**
- 6 Minute Walk Test — **Fatigue/slowness/ inactivity**
- Digit Symbol Substitution Test — **Slowness**
- Pittsburgh Fatiguability Scale — **Fatigue**

Vigor to Frailty As a Continuum—A New Approach in the Study of Muscle, Mobility, and Aging Cohort

Anne B. Newman, MD, MPH,[1,*] Terri L. Blackwell, MA,[2] Theresa Mau, PhD,[2,3] Peggy M. Cawthon, PhD,[2,3] Paul M. Coen, PhD,[4] Steven R. Cummings, MD,[2,3] Frederico G.S. Toledo, MD,[5] Bret H. Goodpaster, PhD,[4] Nancy W. Glynn, PhD,[1] Russell T. Hepple, PhD,[6] and Stephen B. Kritchevsky, PhD[7]



Vigor to Frailty (0-12) as a Continuum in SOMMA

Summary

Pilot studies establish the foundation for follow up work:

- Safety in older adults
- Tolerance and feasibility
- Older adult specific PK and PD
- Early signs of mechanism
- Early signs of clinical efficacy

Buck

Thank you!

Collaborators:

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George Kuchel, MD

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Mitsunori Nomura, PhD

Chatura Senadheera*

Wendie Silverman-Martin, RN*

Elizabeth Stephens* (*clinical team)

Current Funding:

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NIA R01 AG081226

CDMRP - W81XWH-22-1-0867

Buck Institute Intramural Funds

Buck Institute Impact Circle

Dr. James Johnson

Protocol

medRxiv
THE PREPRINT SERVER FOR HEALTH SCIENCES

Kinetic data

medRxiv
THE PREPRINT SERVER FOR HEALTH SCIENCES

Tolerability/ safety data

medRxiv
THE PREPRINT SERVER FOR HEALTH SCIENCES

https://clinicaltrials.gov/study/NCT05585762

Buck

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PUBLIC COMMENT DEBRIEF

PUBLIC COMMENT DEBRIEF

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Academy of Health & Lifespan Research; Albert Einstein College of Medicine

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UCLA and Stanford Medicine

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