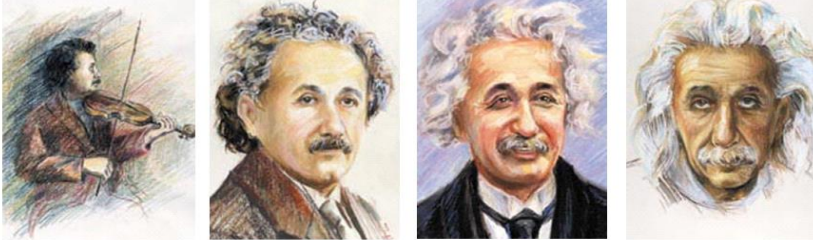




Albert Einstein College of Medicine

Montefiore

EINSTEIN'S INSTITUTE FOR AGING RESEARCH



*Staying healthy as we get older!*

Nir Barzilai, M.D.

Professor of Medicine and Genetics  
Director: Institute for Aging Research

PI: The E-Nathan Shock Center  
The E-Glenn Center for the  
Biology of Human Aging

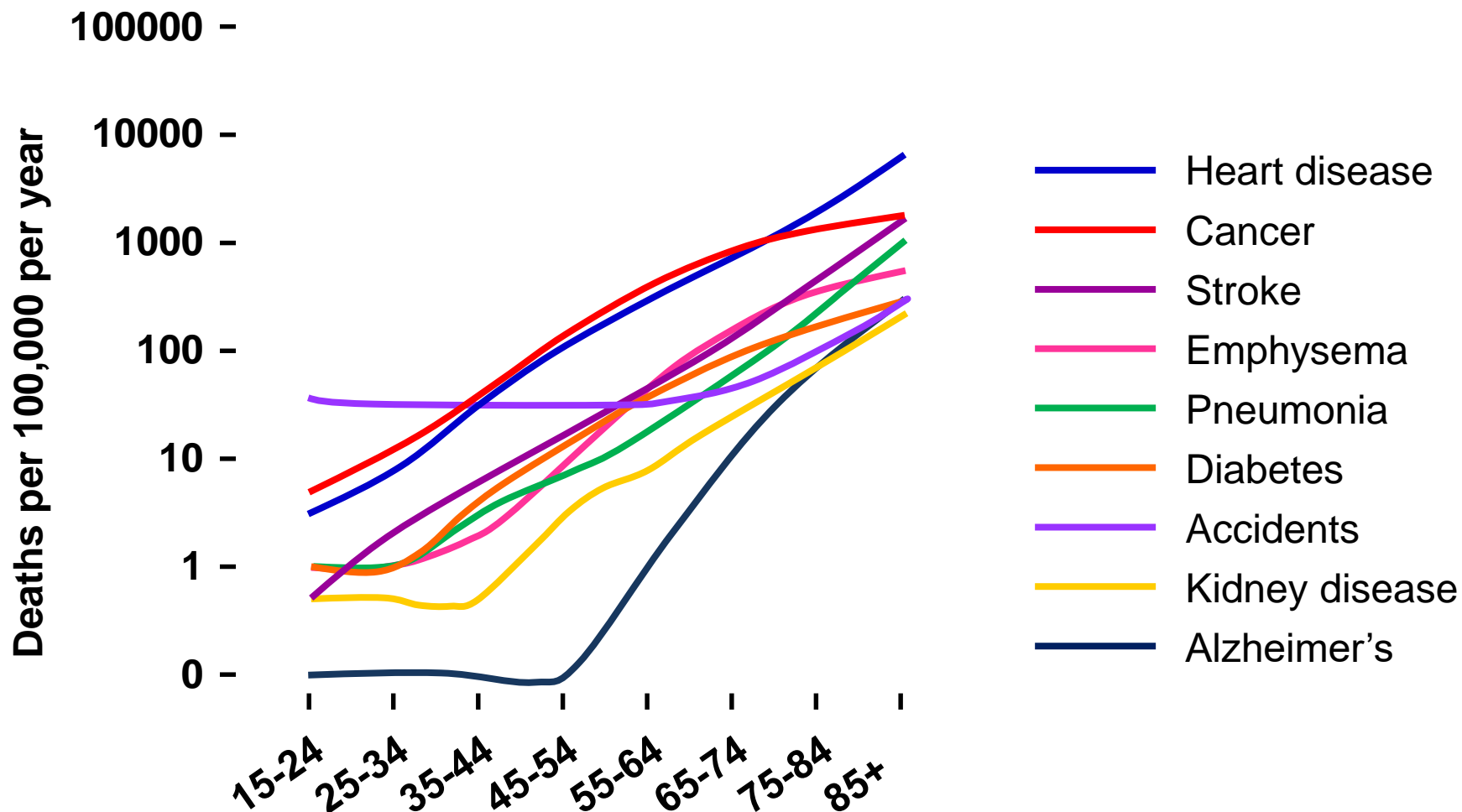
NMRC-2019

**How to die young at a very old age**

**Chronological vs. biological age**

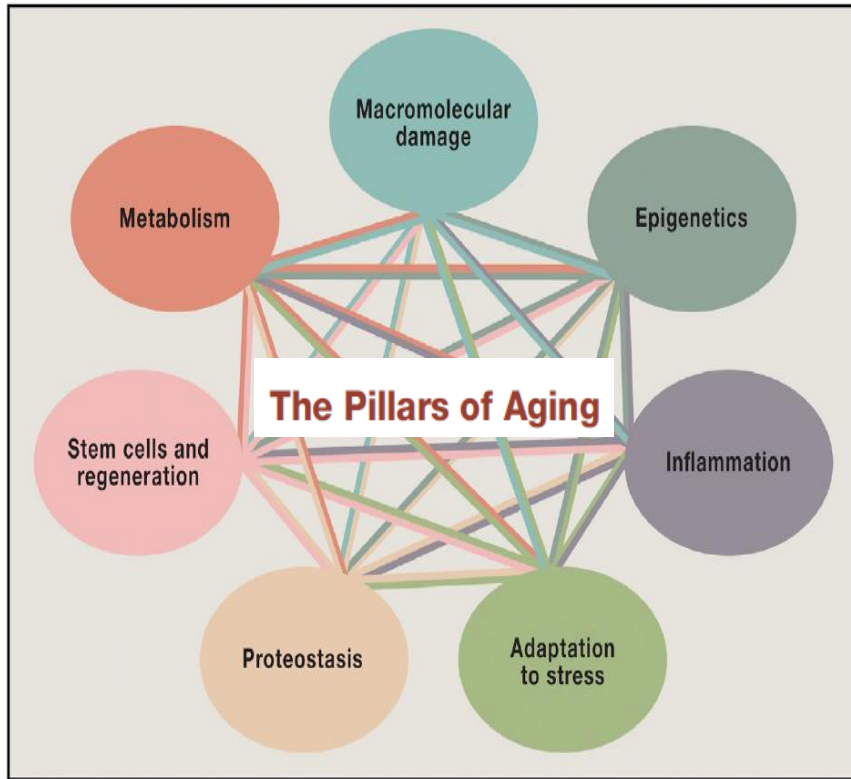
# Aging is the major risk for age related diseases: Aging drive diseases!

(The Milbank Quarterly, Vol. 80, No. 1, 2002 from 1997 U.S. Vital Statistics)

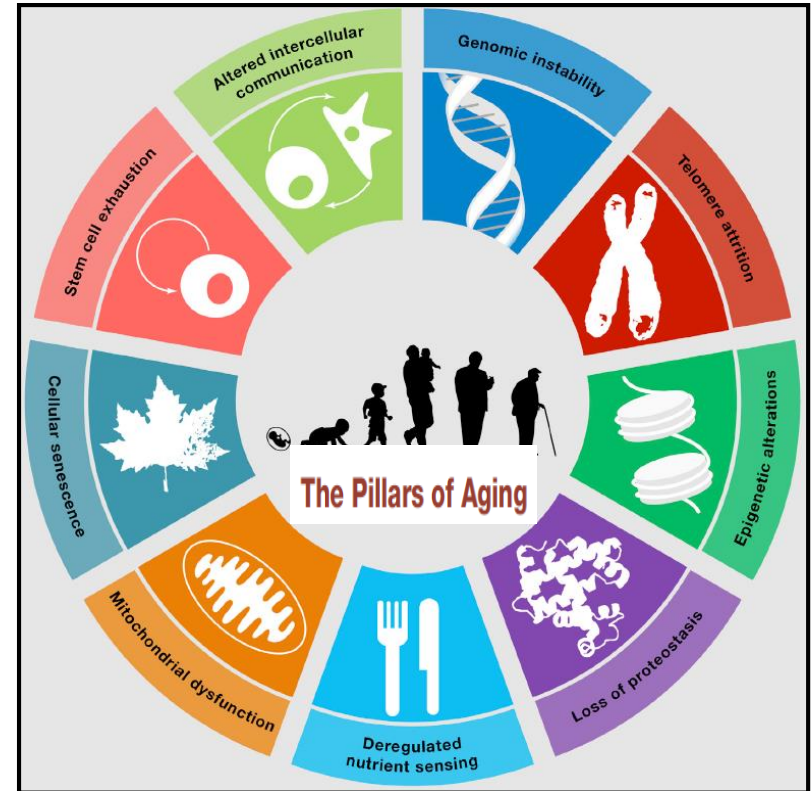


**Genetics and environment of the individual  
determine which disease occurs first**

# What is the evidence for success in the goal of delaying aging?



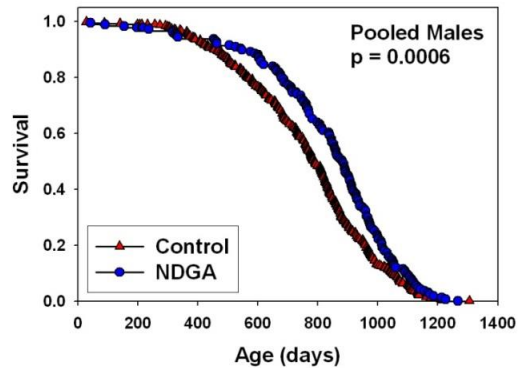
Kennedy et al. Cell (2014)



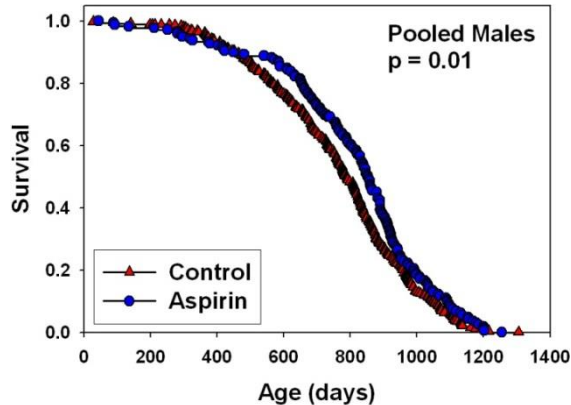
Lopez Otin et al. Cell (2013)

- **Healthy** lifespan has been extended in numerous animal models.
- Relevant drugs have been used in humans.  
**(Metformin, Rapamycin....)**

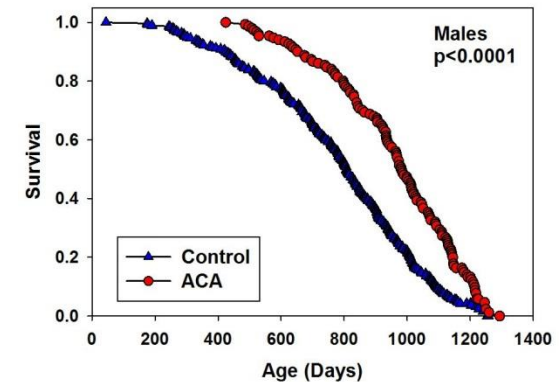
# Intervention Testing Program (NIA)



**NDGA**  
(Nordihydroguaiaretic acid)

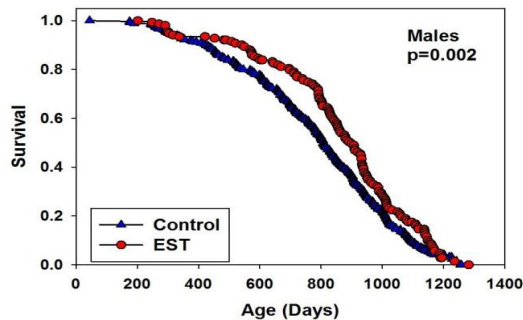


**Aspirin**

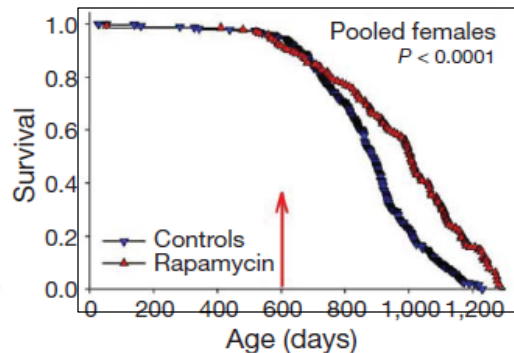


**Acarbose**

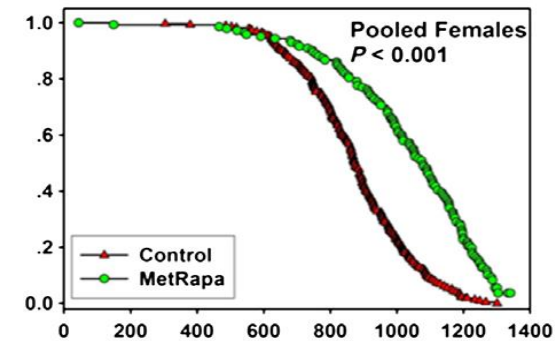
Age (Days)



**17- $\alpha$  estradiol**



**Rapamycin**



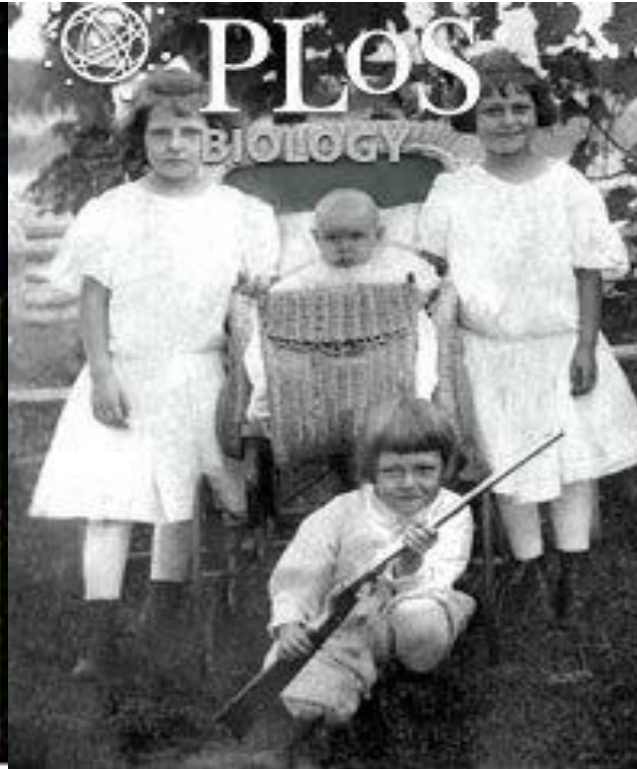
**Rapamycin+  
metformin**

# Meet the Kahn siblings

~90 years later



~1920



**Cover of PLoS Biology April 2006**

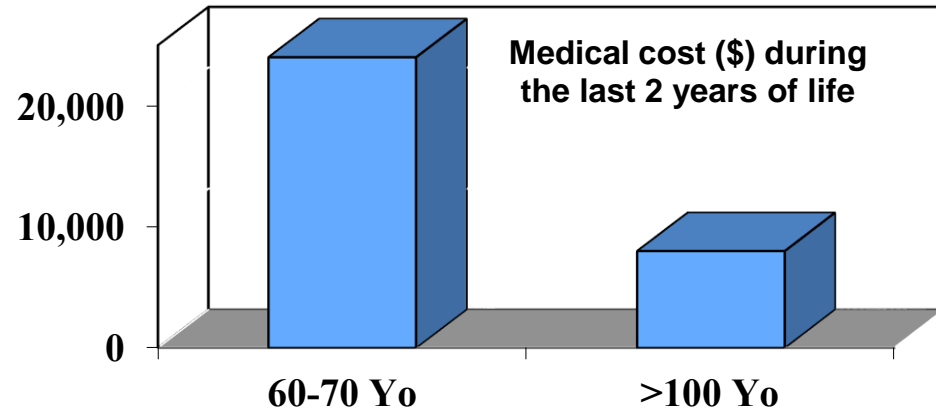
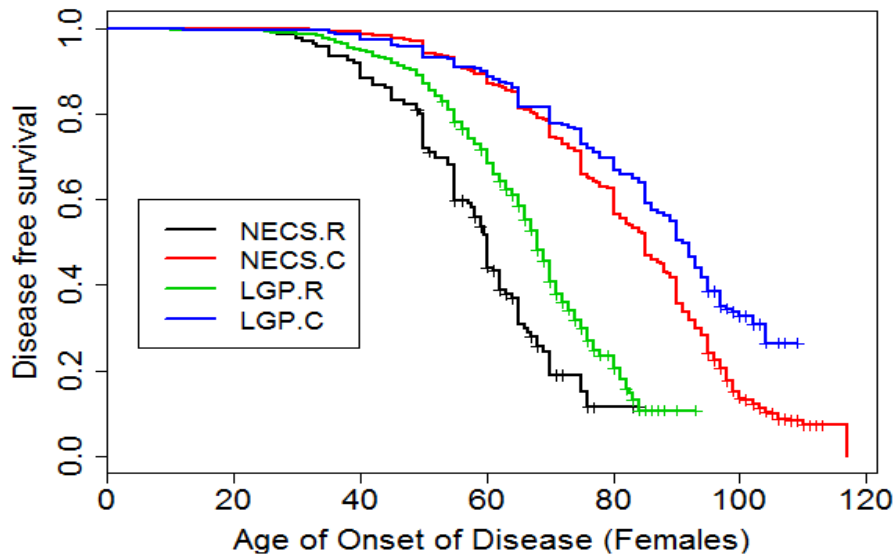
Atzmon et al. PLoS Biol 2006

# Longevity studies

- Being centenarian is a rare occurrence!
- There is a remarkable family history of exceptional longevity **and health span** in parents, siblings and offspring of “centenarians”.
- **LGP**: n~700 centenarians, 95-112; Offspring and unrelated control (no family history of longevity) n~1200;
- **LonGenity**: n~700 offspring and n~700 unrelated control)
- A homogenous population of Ashkenazi Jews (AJs).
- **We have (core use; unidentified):** Demographic and health data and, whole exome + genome sequencing, CD34, T & B cells, lymphoblasts, proteomics, metabolomics, epigenetics (microRNA and methylations).

# Lifespan & health span

**Diseases include:** Cancer, CVD, Diabetes, Hypertension, Dementia, Osteoporosis

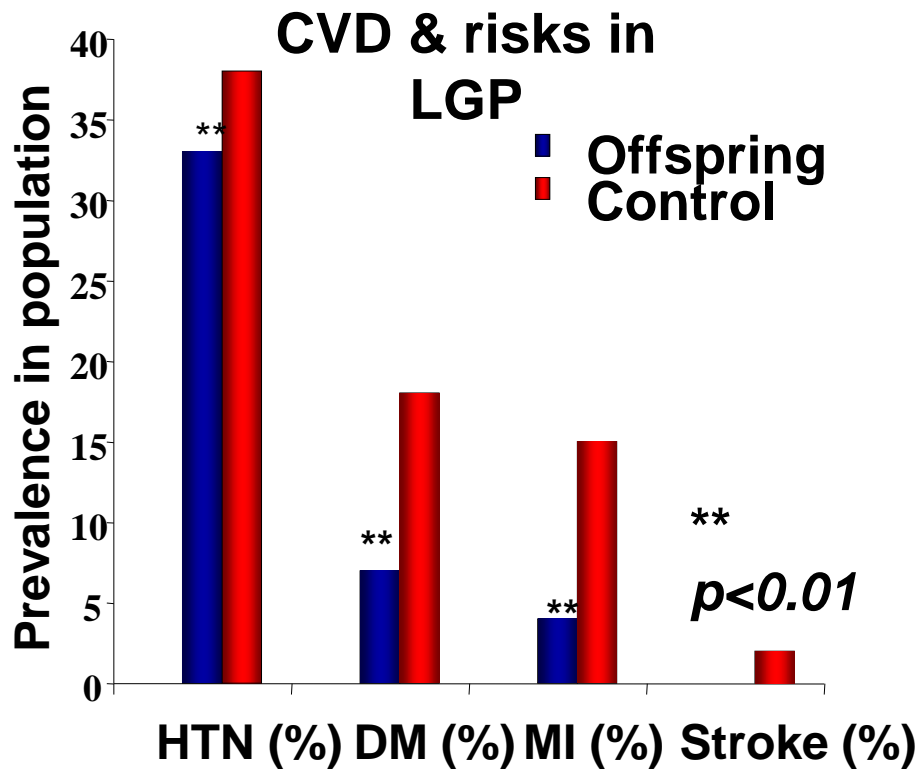


J Am Geriatr Soc. 2016 Jul 5

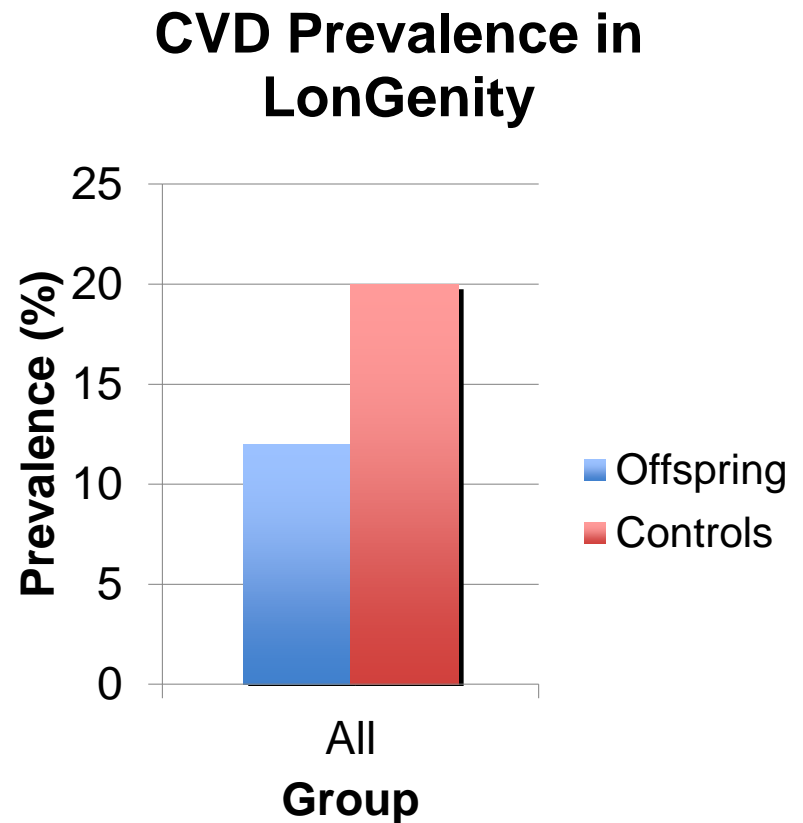
**Longevity Dividend**

# Heritability of health-span (not lifespan)

## Chronological vs. biological age



JAGS 2004; 52:274

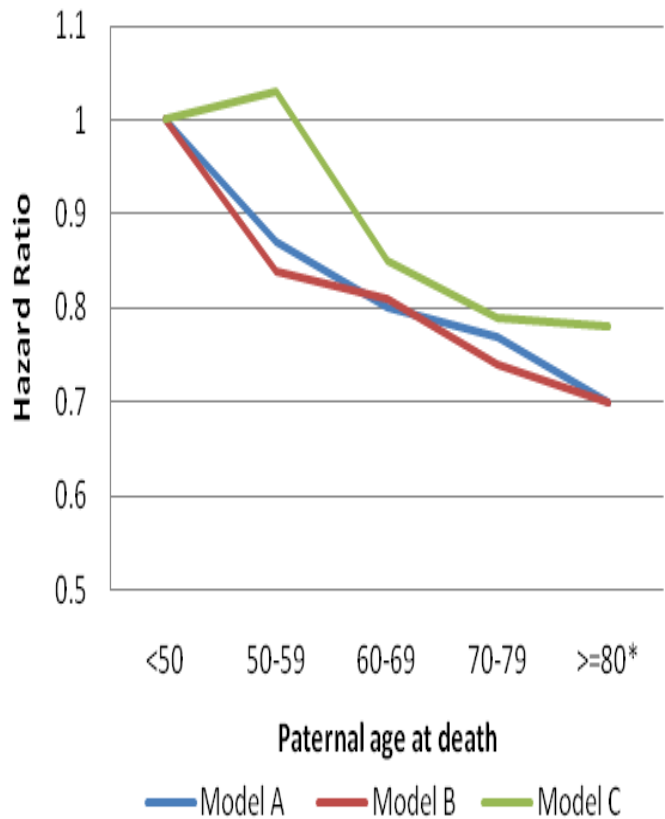


Am J Cardiol. 2017; 9149(17)

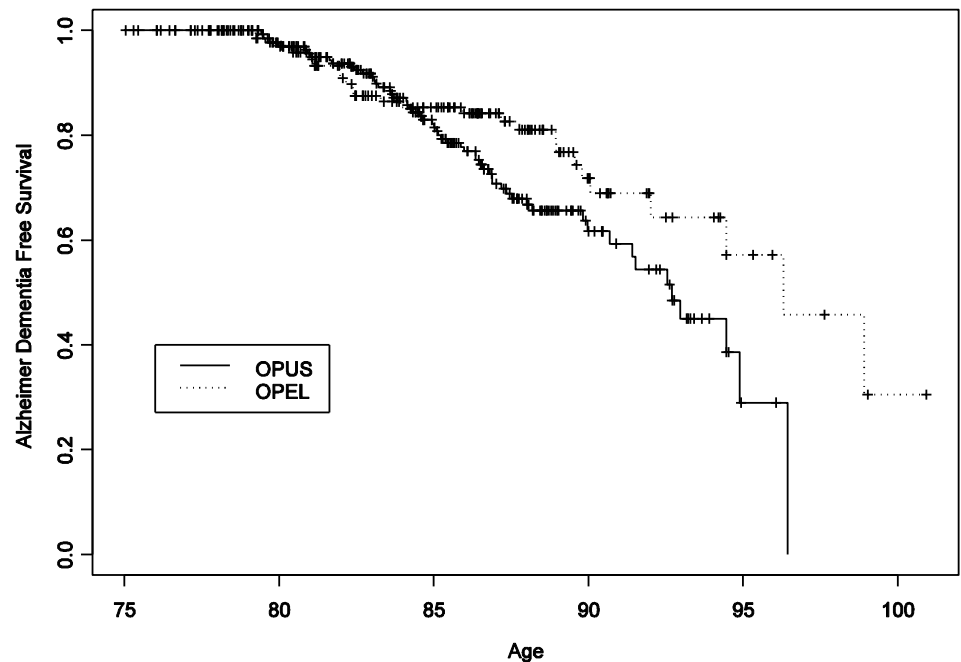


# If a parent has longer life is his offspring healthier for longer?

## Diabetes risk (DPP)



## AD and memory decline (EAS)



# Hypothesis for genetics of centenarian

- 1) Interaction with the environment.**
- 2) Perfect genome.**
- 3) Longevity (Protective/resilience) genotypes**

# Centenarians and interaction with the environment

'Environmental' risk	Centenarians		NHANES1	
	Men	Women	Men	Women
•Over weight/obese:	48%	44%	•55%	41%
•Smoking:	60%	30%	•75%	26%
•Alcohol (daily):	24%	12%	•22%	11%
•Physical activity:	43%	47%	•57%	44%
(Moderate: regular walking, bicycling, housework)				
•Vegetarians: 2.6%				

# Do centenarians have a perfect genome?

## WGS of 44 AJs centenarians:

ClinVar database ~15,000 pathogenic variants

A total of 227 autosomal and seven X-chromosomal coding SNVs.

**Parkinson-** 2 mutations in L444P (GAB)

**AD-** **APOE4**, *UBQLN2* (also ALS)

**Other degenerative-** *SEMA4A*, *RP1*, *FZD4*, *MYO1A*, *CYP1B1*, *VSX1*, *WDR36*

**Neoplastic-** *APC*, *BRCA1*, *RET*, *RNASEL*, and *STK11*

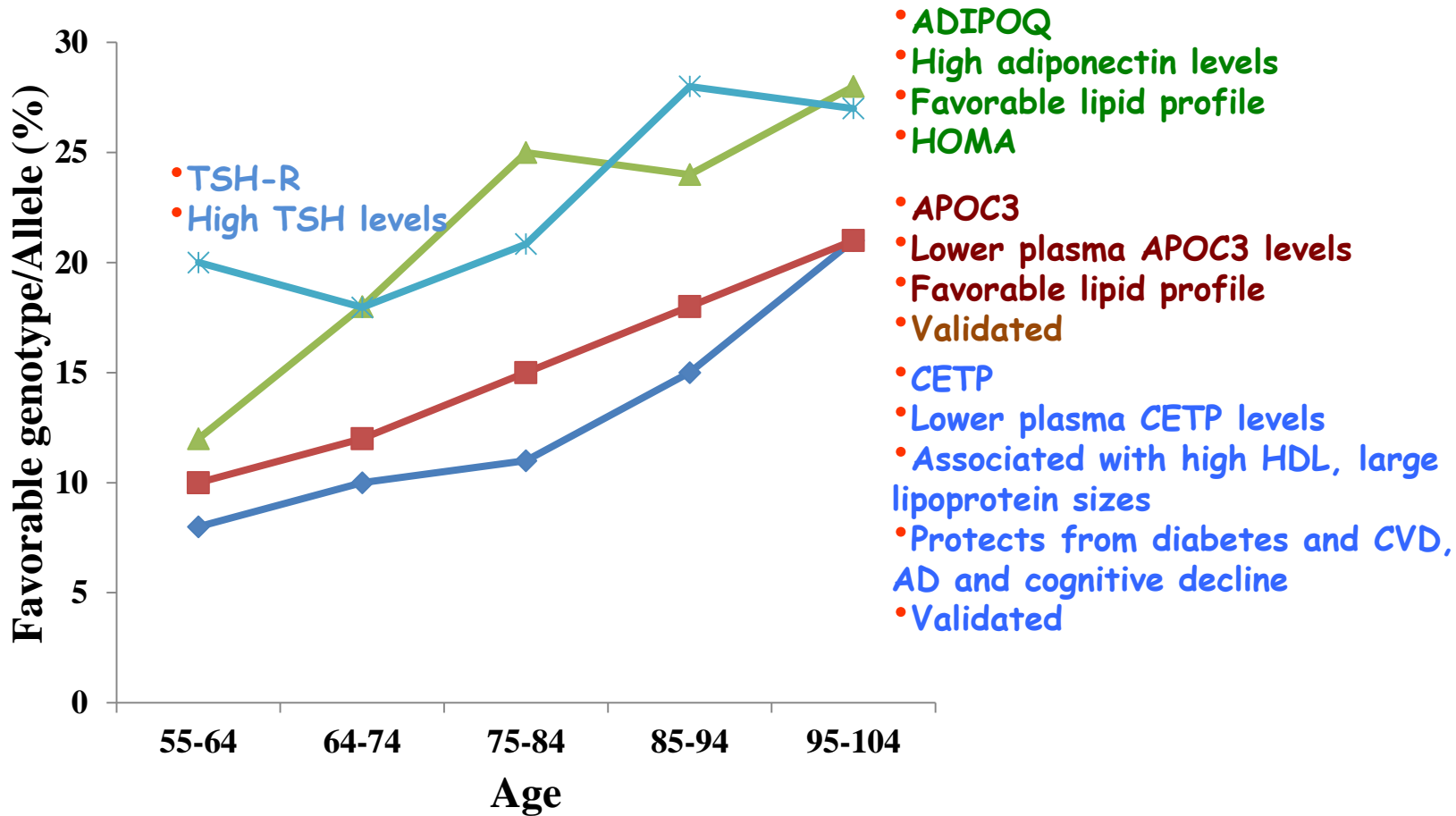
**Cardiac (dominant)-** *ABCC9*, *ACTN2*, *ANK2*, *CACNA1C*, *JPH2*, *KCNE2*, *MYL2*, and *TMEM43*

**Other dominant-** 18 variants for autosomal-dominant diseases and 6 mutations for X-Chromosomal diseases

**Other recessive-** 72 variants for recessive traits include four variants that have least one homozygous

Similar prevalence of common SNPs for age-related disease

# Candidate Gene Approach



**Impact!!!**

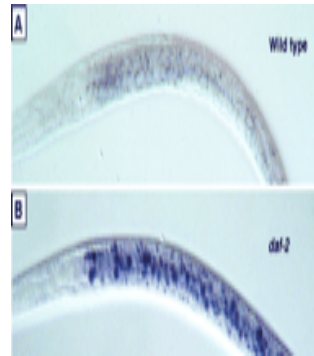
Phase 3 trial successful: **Merck**, **Ionis**

Change in medical practice **TSH**

# Candidate Gene Approach: GH/IGF-1 signaling pathway



Small dogs live longer than large dogs



Longer lifespan in *daf-2* mutants

## Genetics of GH/IGF-1:

IGF-1-R	2%
d3GHR	12%
FOX3A	22%
MicrRNA	33%

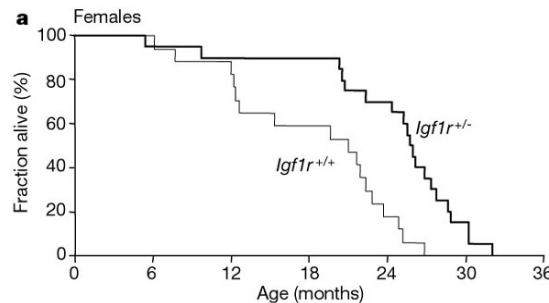
Total > 60%



*Ghr*<sup>-/-</sup>, *lit/lit*, GHA, Wt, *bGH*  
 ↑ Longevity ↓



Ponies live longer than thoroughbreds



*IGF-1R*<sup>+/-</sup>-females

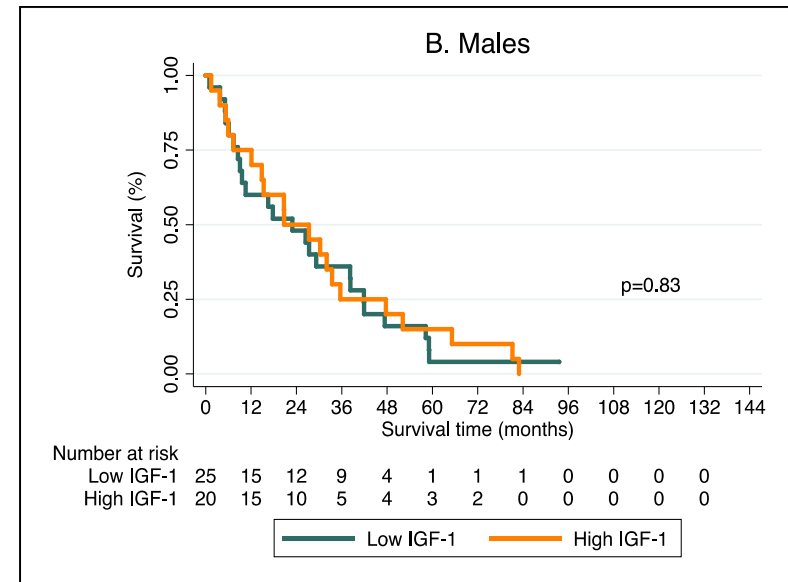
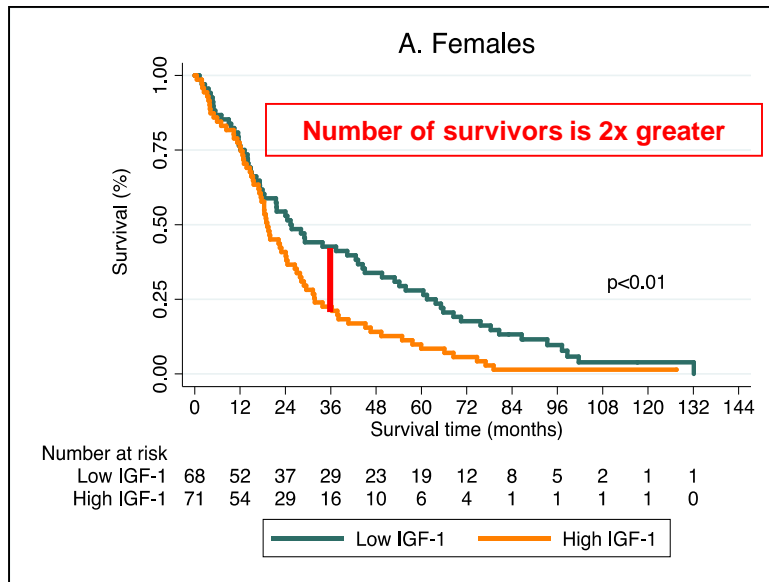


Snell AMES mice

# Lower IGF-1 levels and survival

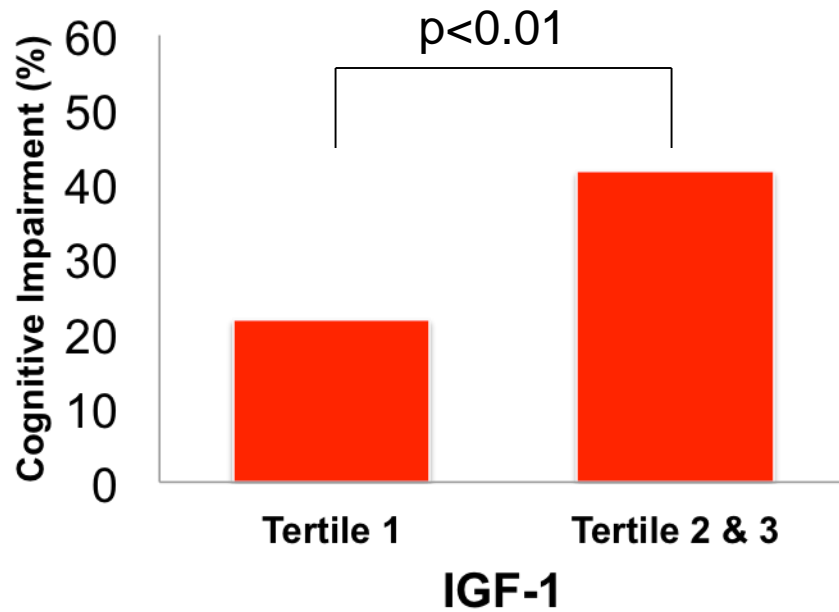


Sofiya Milman, MD

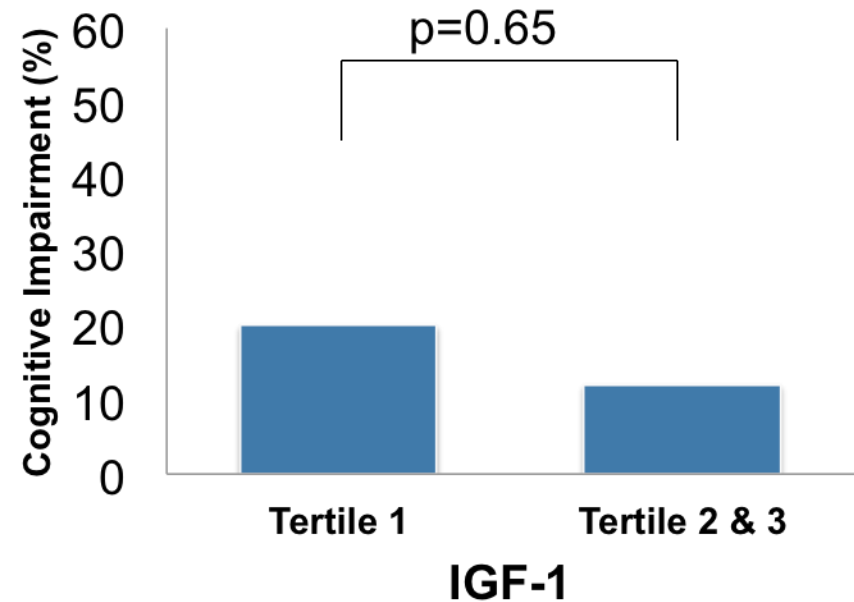


# Lower IGF-1 levels and Cognition

## Females



## Males



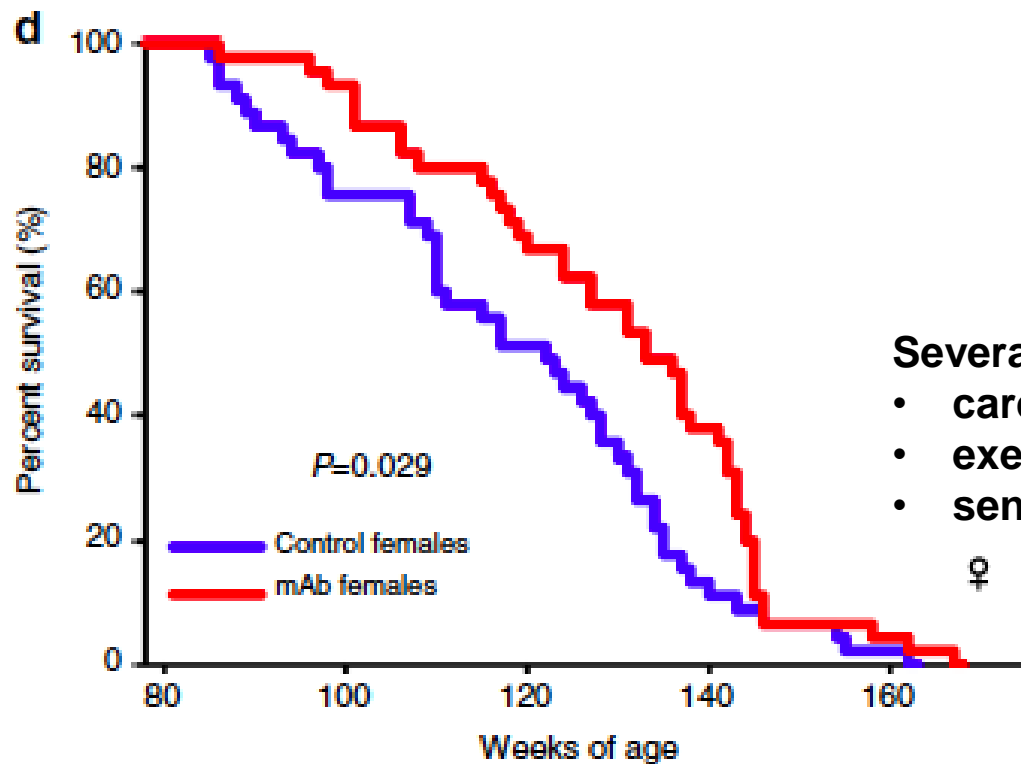
**Muscle function is unchanged between groups.**



# Treatment with IGF-1R antibody



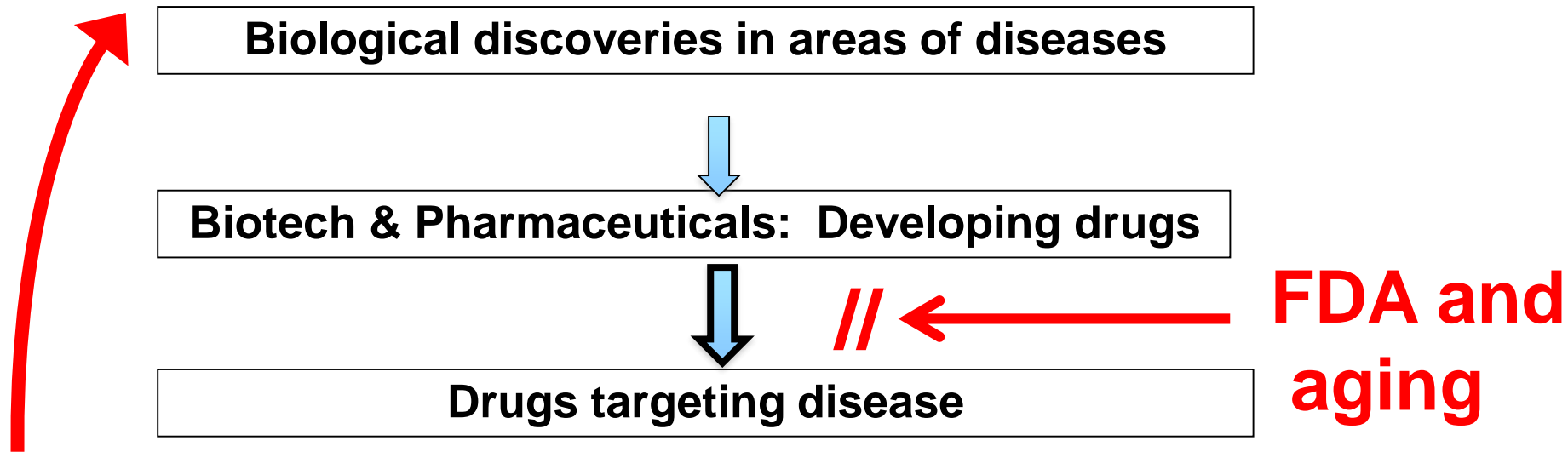
Derek Huffman, PhD



Several health span domains were improved:

- cardiac function
- exercise capacity
- sensorimotor function

# Challenges to translate our advance in understanding aging to humans?



If a drug has no indication:

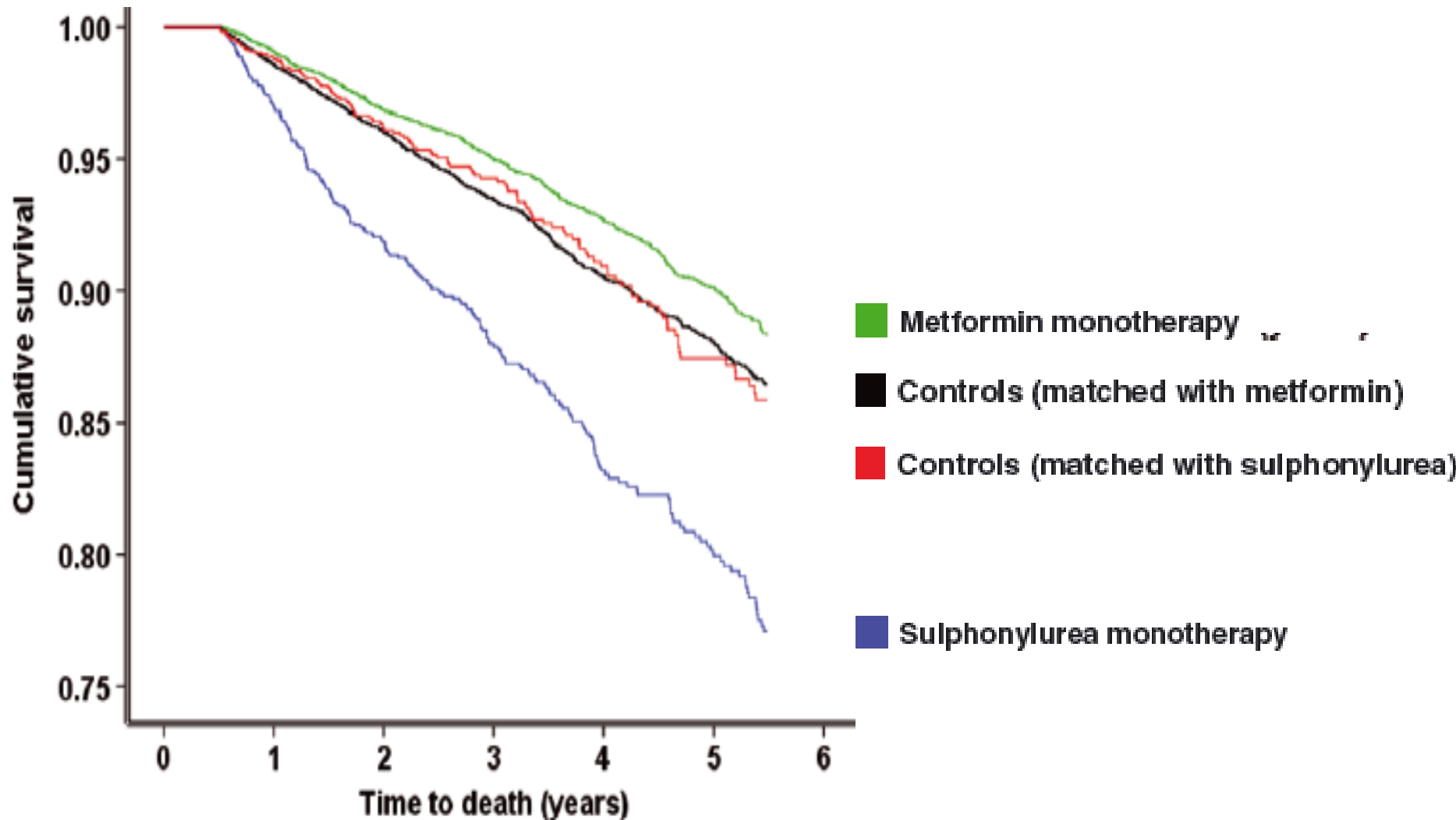
- 1) Healthcare provider would not pay for their clients.
- 2) Pharmaceuticals will not develop other, better and combination of drugs.

# Substantial effects of metformin on health-span in humans:

- **Intervention in non-type 2 diabetes mellitus (T2DM):** Metformin delays T2DM (DPP).
- **Intervention:** Metformin delays CVD (UKPDS) in T2DM.
- **Association:** Metformin is associated with less cancer in patients with T2DM.
- Early support exists that metformin may delay cognitive decline and AD, even in non-T2DM.
- **Phase 4:** lower mortality in patients with T2DM on metformin compared with non-diabetics.

**Metformin is a tool to target aging**

# Metformin decreases mortality in T2DM and in non-diabetics

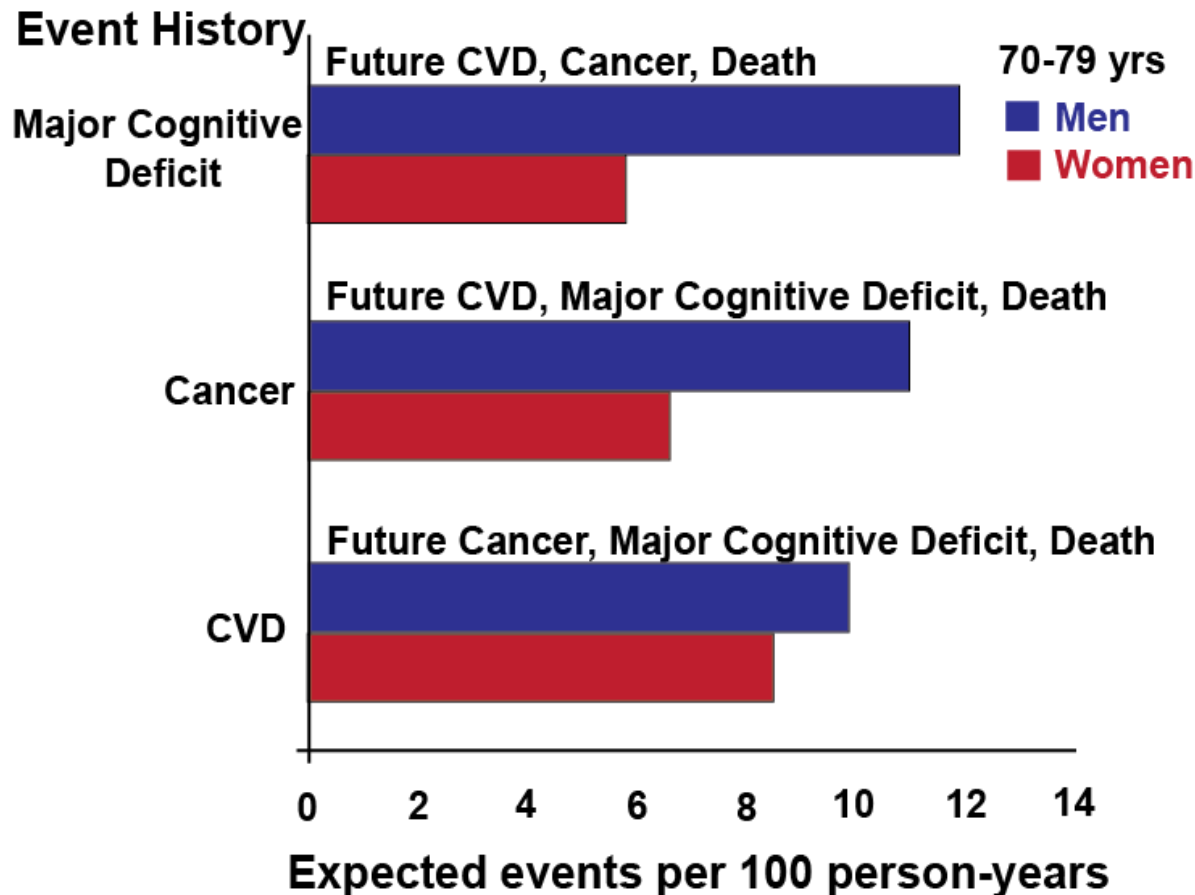


# Targeting Aging with Metformin (TAME)

---

- **(Proof of concept)** To show that composite of age-related diseases can be prevented by metformin
- **(FDA regulation)** To obtain a new indication for the delay of age-related morbidities.

# Health ABC event rates for chronic conditions grouped by history



\*Courtesy of Tamara Harris, preliminary data for TAME

# TAME study design overview

**Age 65-80 AND  
Gait speed 0.4-1 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.**

\*excluding prostate and non-melanoma skin cancer

Primary  
Outcome

**(Functional) Time to incidence of disability:** Major decline in mobility or cognitive function, onset of severe ADL limitation.

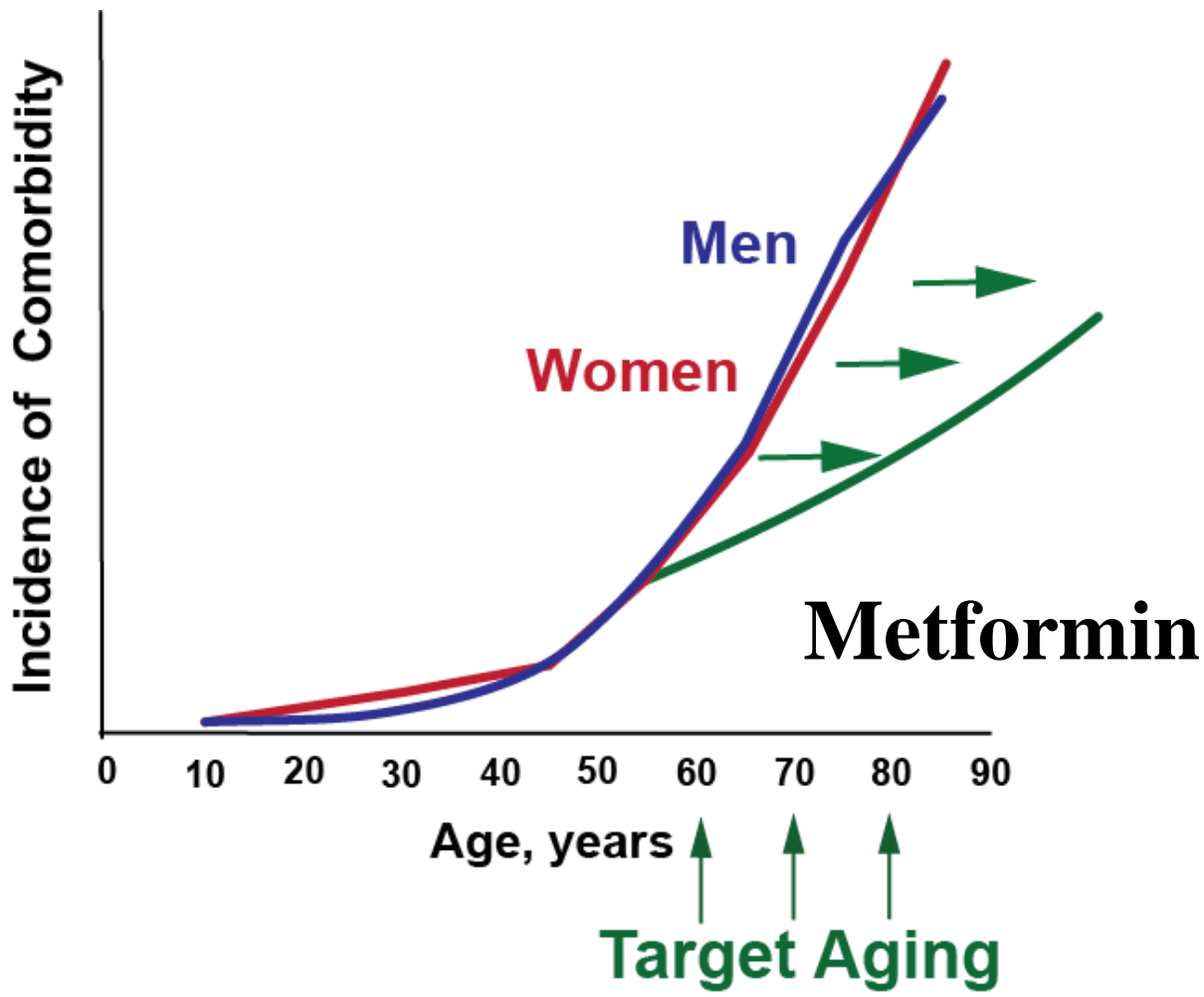
**Supporting analyses:** Change in patient-centered outcomes, and continuous measures of physical and cognitive performance.

Secondary  
Outcome

**(Biological) Change in metformin levels and biomarkers of aging and age-related diseases.** To provide convergent evidence of broad age-related effects while establishing a resource for innovation and discovery of emerging biomarkers.

Tertiary  
Outcomes

# Metformin as a tool to get better drugs: Changing the face of aging





# Targeting aging: Why Singapore?

- Not all medications (like metformin?) are as good as others (like acarbose?) in Asians.
- Longevity Dividends can be realized earlier in an organized country with health care that is working.
- Singapore attracts the best scientists in our field (leadership-Dean Yap-Seng Chong, Brian Kennedy, Jeff Halter)
- Opportunity for business of aging (biotech etc)

# Blactocytes erase aging!



JEFF JOHNSON

BIOLOGICAL & MEDICAL VISUALS

# Time in a bottle

If I could save time in a bottle  
The first thing that I'd like to do  
Is to save every day  
Till eternity passes away  
Just to spend them with you

If I could make days last forever  
If words could make wishes come true  
I'd save every day like a treasure and then  
Again, I would spend them with you

[Jim Croce - Time In A Bottle Lyrics | MetroLyrics](#)

# (Partial list of) collaborators/friends

## Longevity Gene Project and LonGenity

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## CohBar team

## Lifbiosciences team

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