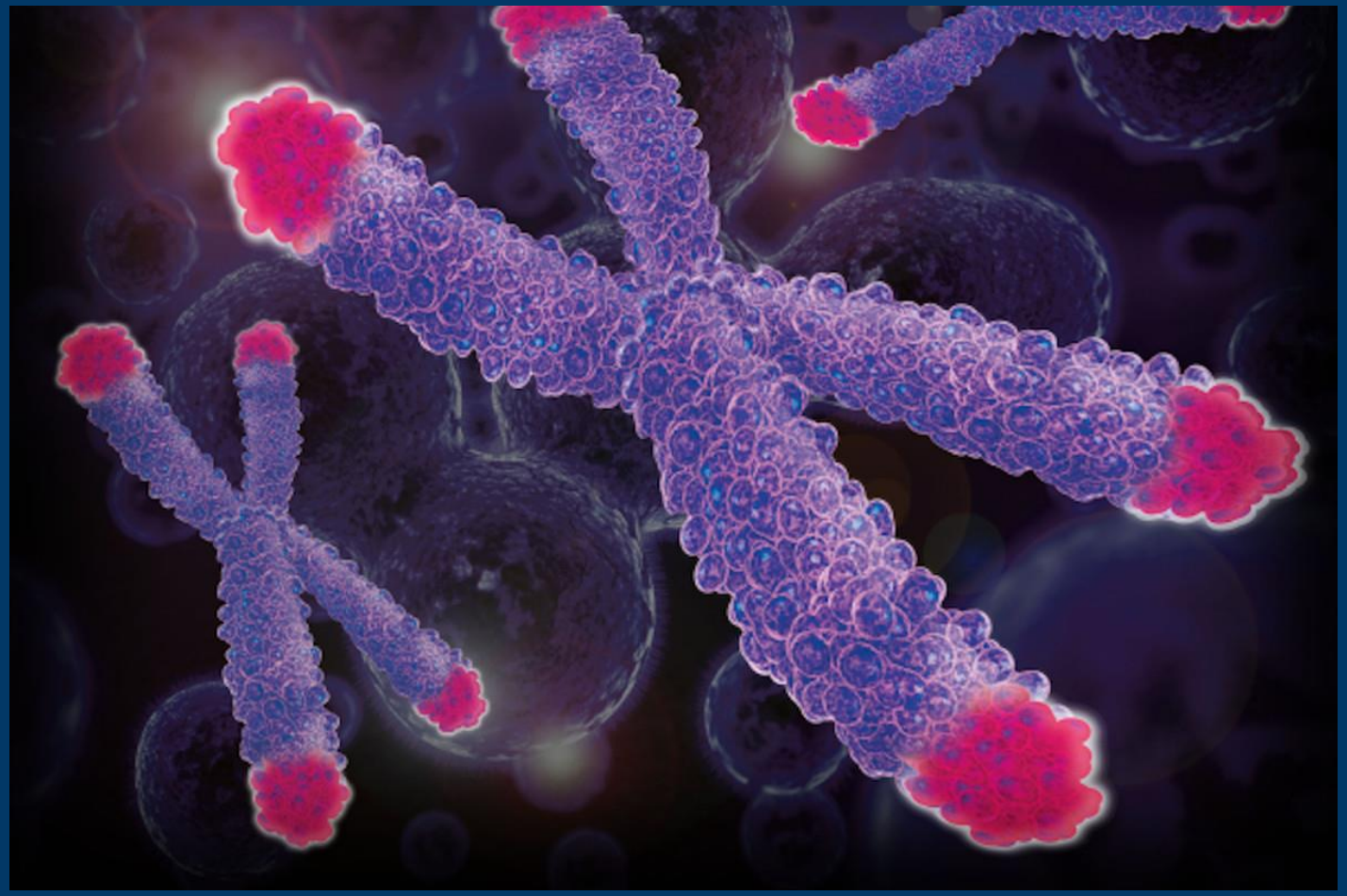
TELOMERES IN 2019

CLINICAL DEVELOPMENTS AND CUTTING-EDGE APPLICATIONS

Joseph Raffaele, MD



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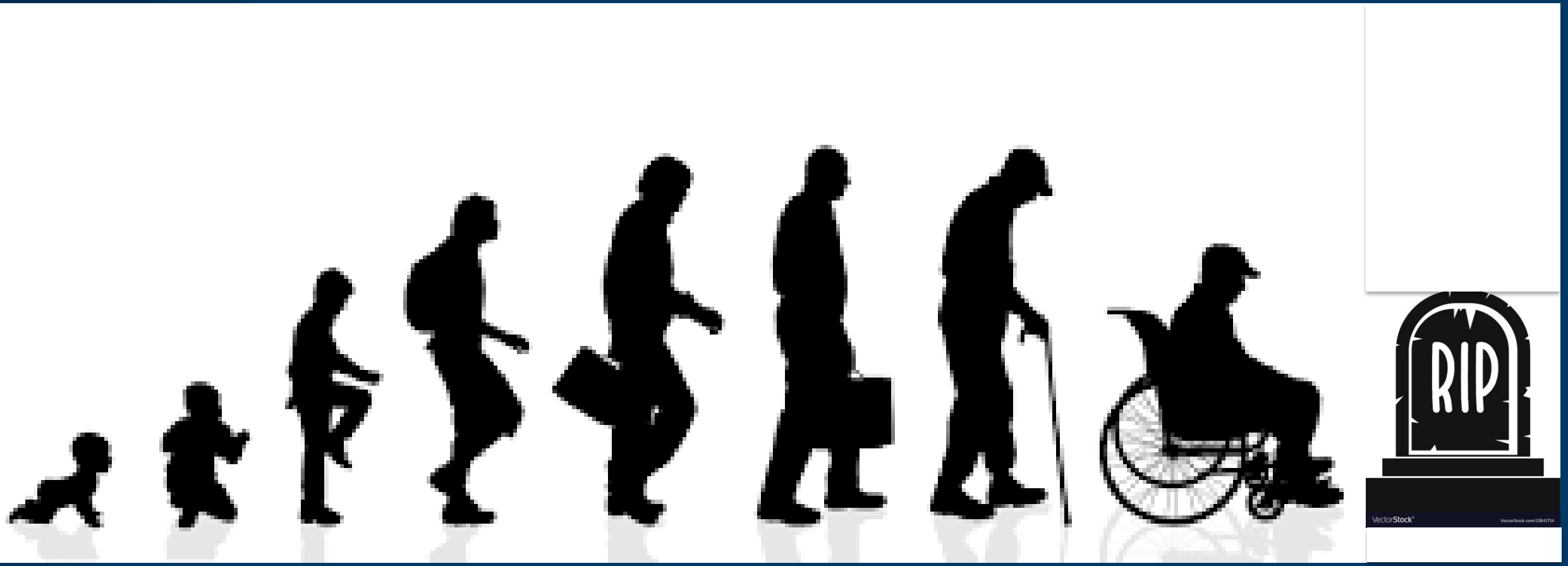
Financial Disclosures

I HAVE NONE

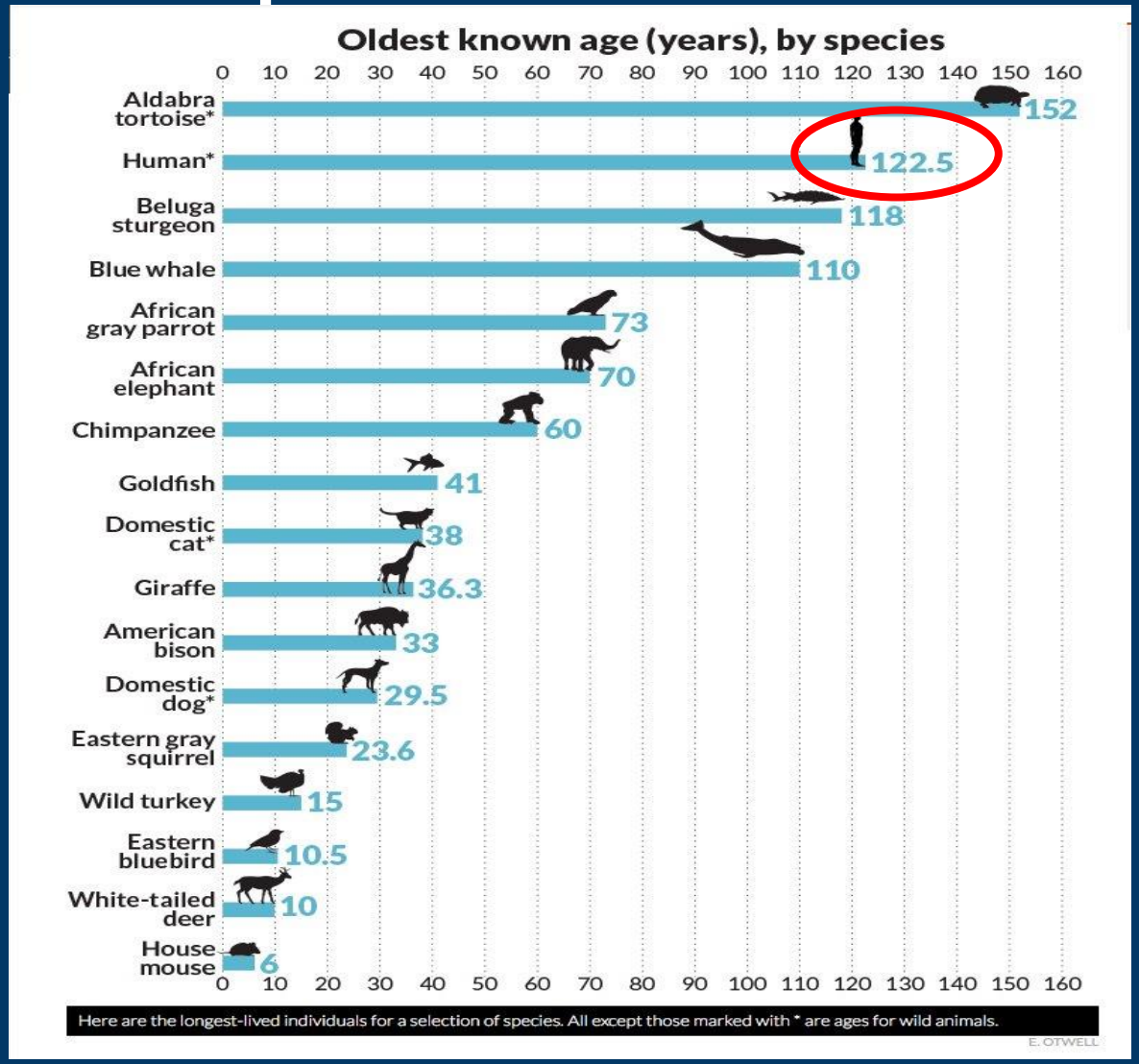
Objectives

- Telomere biology and the 9 Hallmarks of Aging
- Telomere length change with age
- Telomeres and uncommon genetic disorders of shortened lifespan
- Telomere length and gene expression
- Mouse models of telomere biology
- Telomeres cardiovascular disease, cancer, and aging
- Telomere length enhancers
- Therapeutic rationale for telomere lengthening in CAD and AD

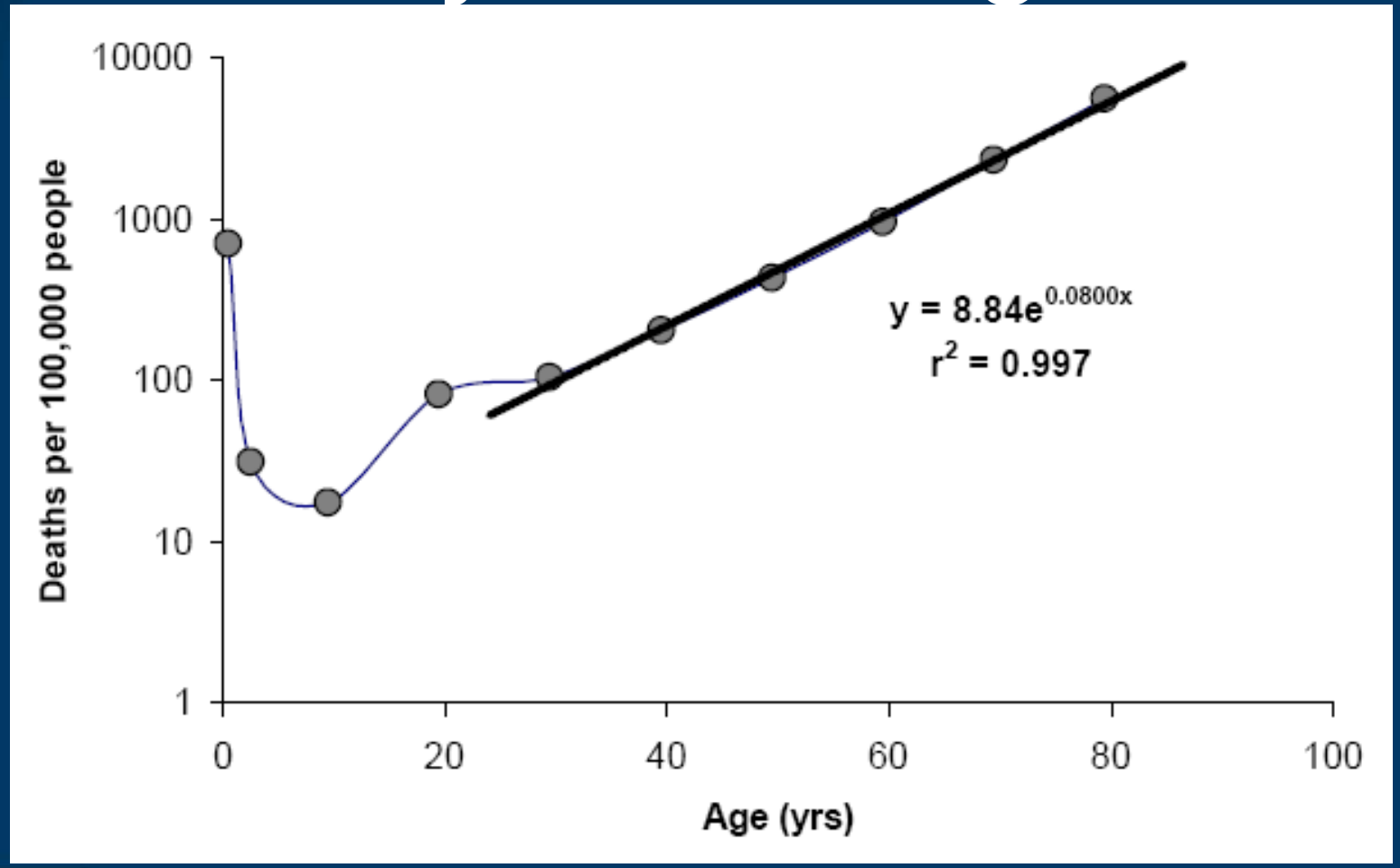
Why do we grow old and die?



Variation in species maximum lifespan



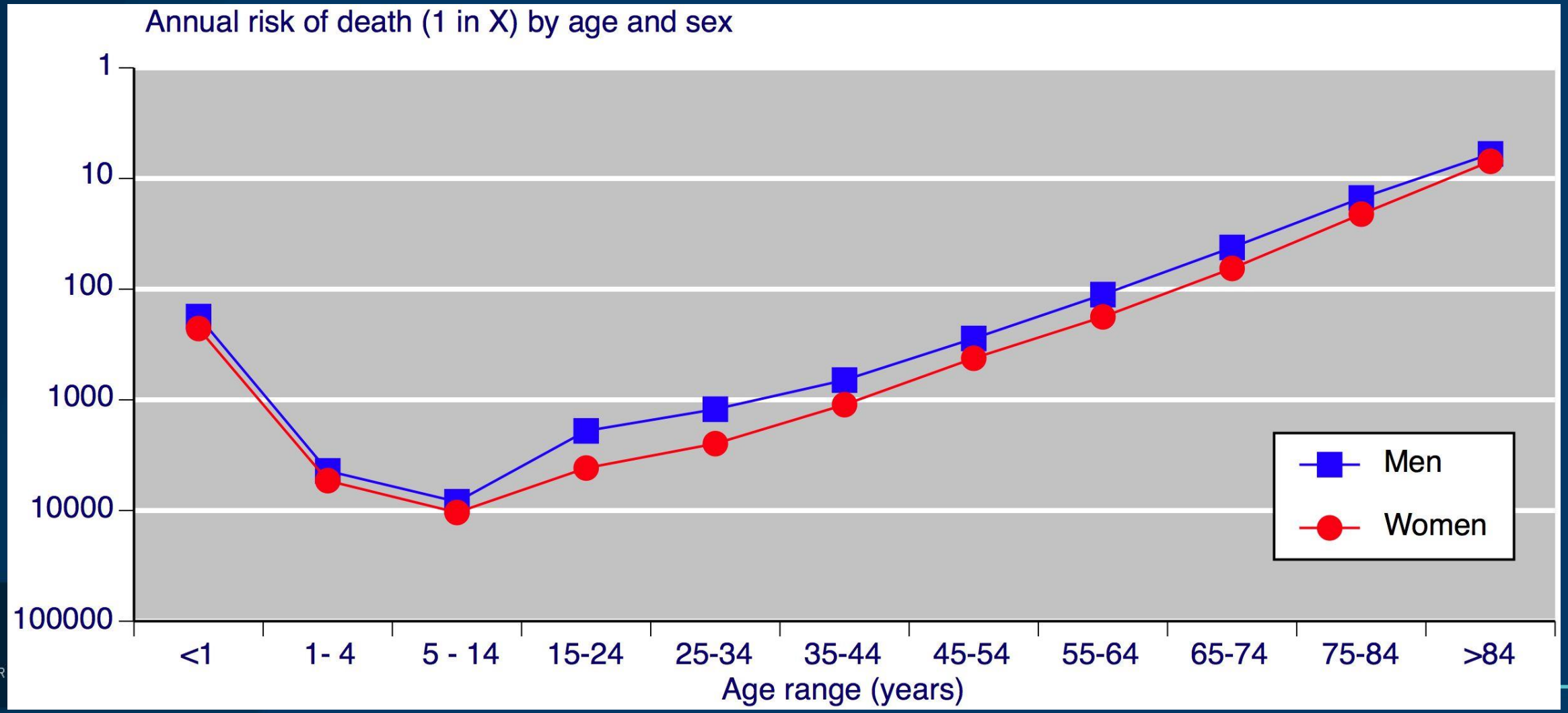
The Mortality Doubling Rate Curve



Mortality doubling rate for humans = 8 years

http://www.senescence.info/aging_definition.html

The Mortality Doubling Curve



122 years

Jeanne Calment: The longest living human

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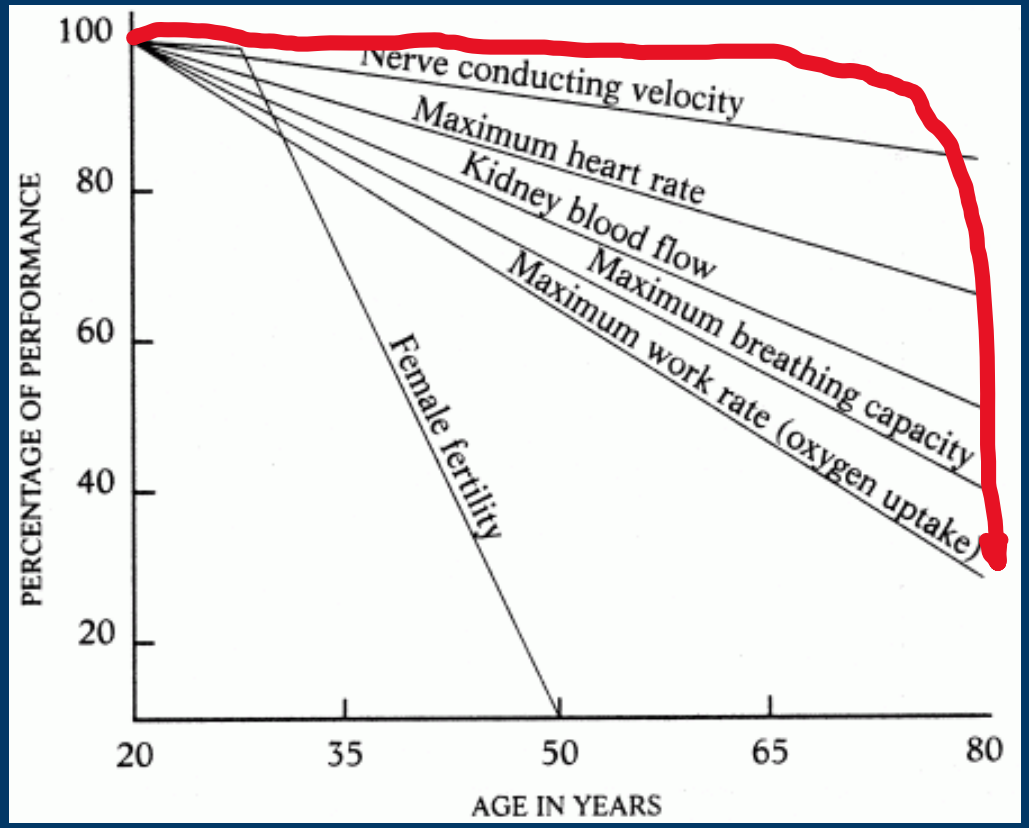
Lifespan ≠ Healthspan

Lifespan = number of years you are alive

Healthspan = number of years you are free of disease
and
You have good physical and mental health

Organ Function Decline with Age



Lifespan Variation: Determined at the level of the Cell

Laboratory Rat

3 years

Naked Mole Rat

32 years

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The Hayflick Limit

- In 1961, Leonard Hayflick overturned a major dictum in biology by showing that cells could not divide indefinitely
- After about 60 doublings, cells in culture either die or just stop dividing
- **The molecular clock is in the telomeres**

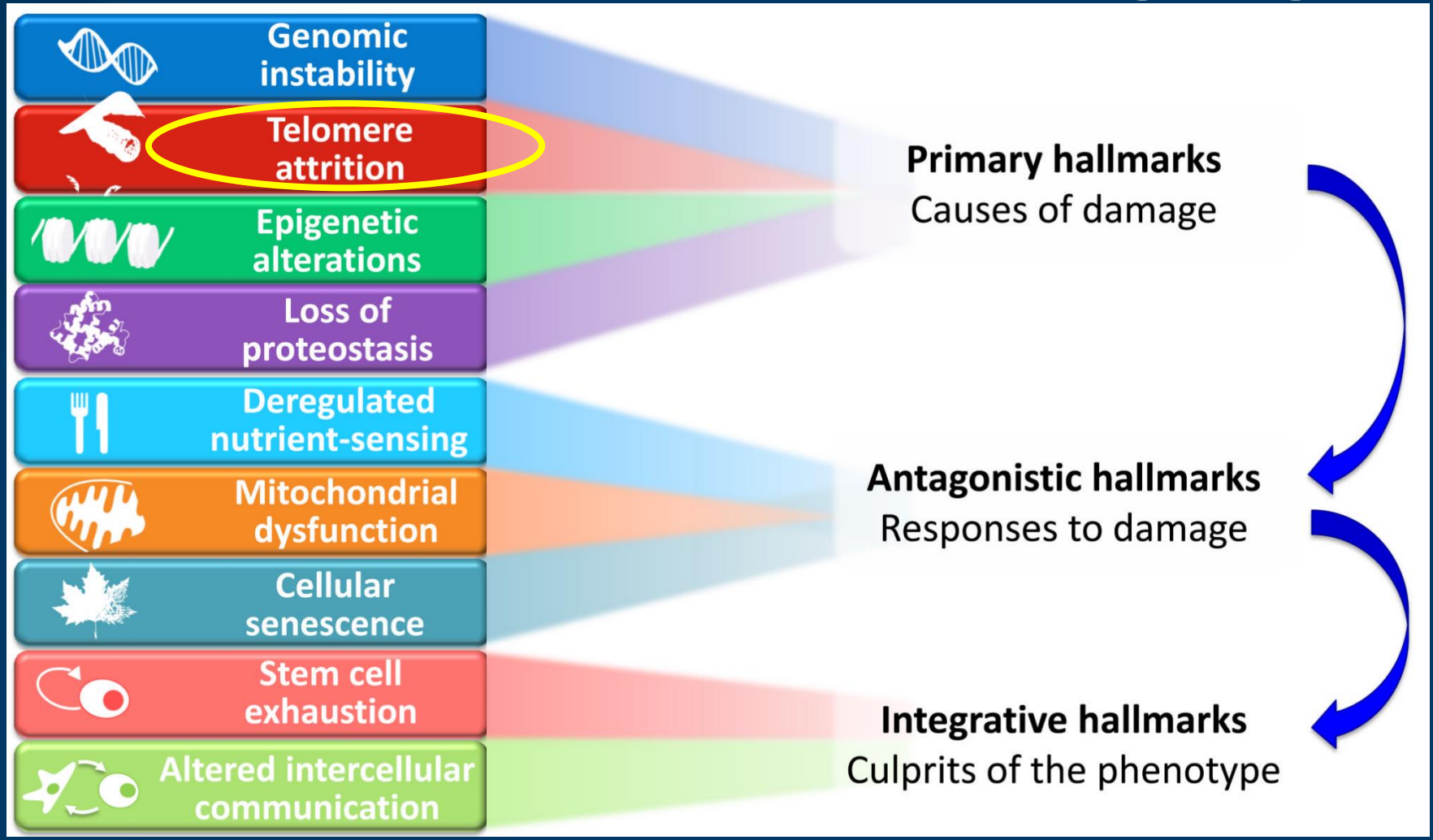
What do Telomeres do?

Protect
Prevent
Proliferate

- Serve as chromosome end-caps to protect the integrity of our genes.
- Keep chromosomes from degrading to prevent fusion and massive genomic instability.
- Allow cells to replicate (the counting mechanism for the Hayflick Limit)

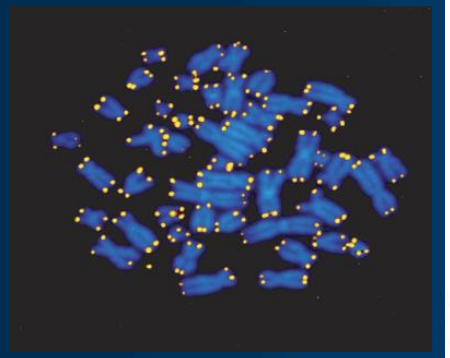
Bottom Line: Telomeres protect cells from DNA mutations, senescence and death.

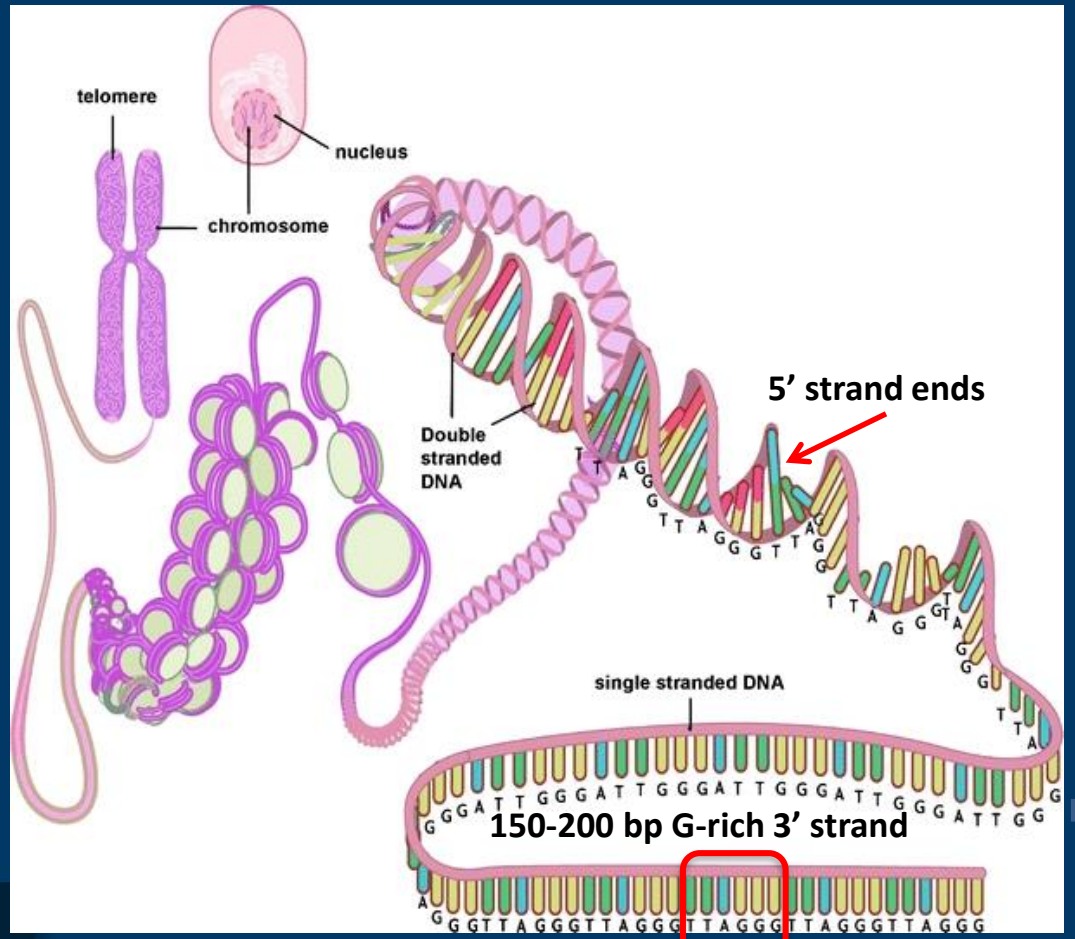
The Hallmarks of Aging



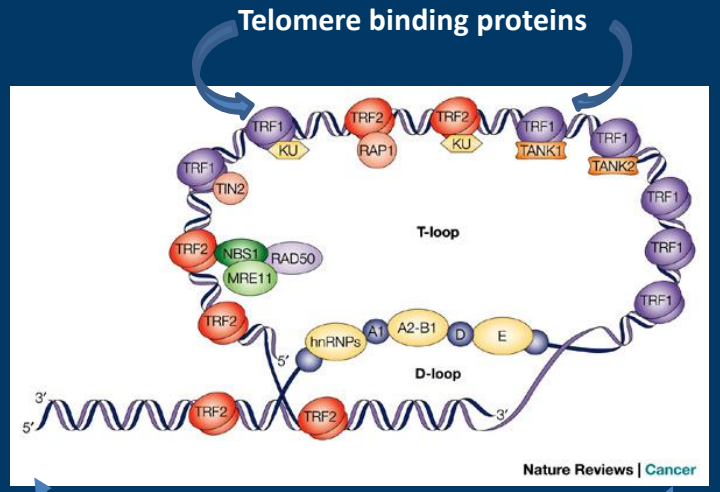
López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The Hallmarks of Aging. Cell. 2013 Jun 6;153(6):1194–217.

How Do Telomeres Work?

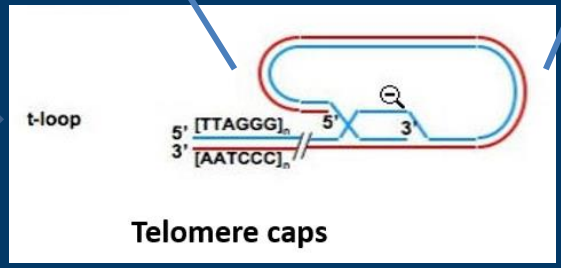




Adapted from Oeseburg Eur J Physiol (2010) 459:259–268



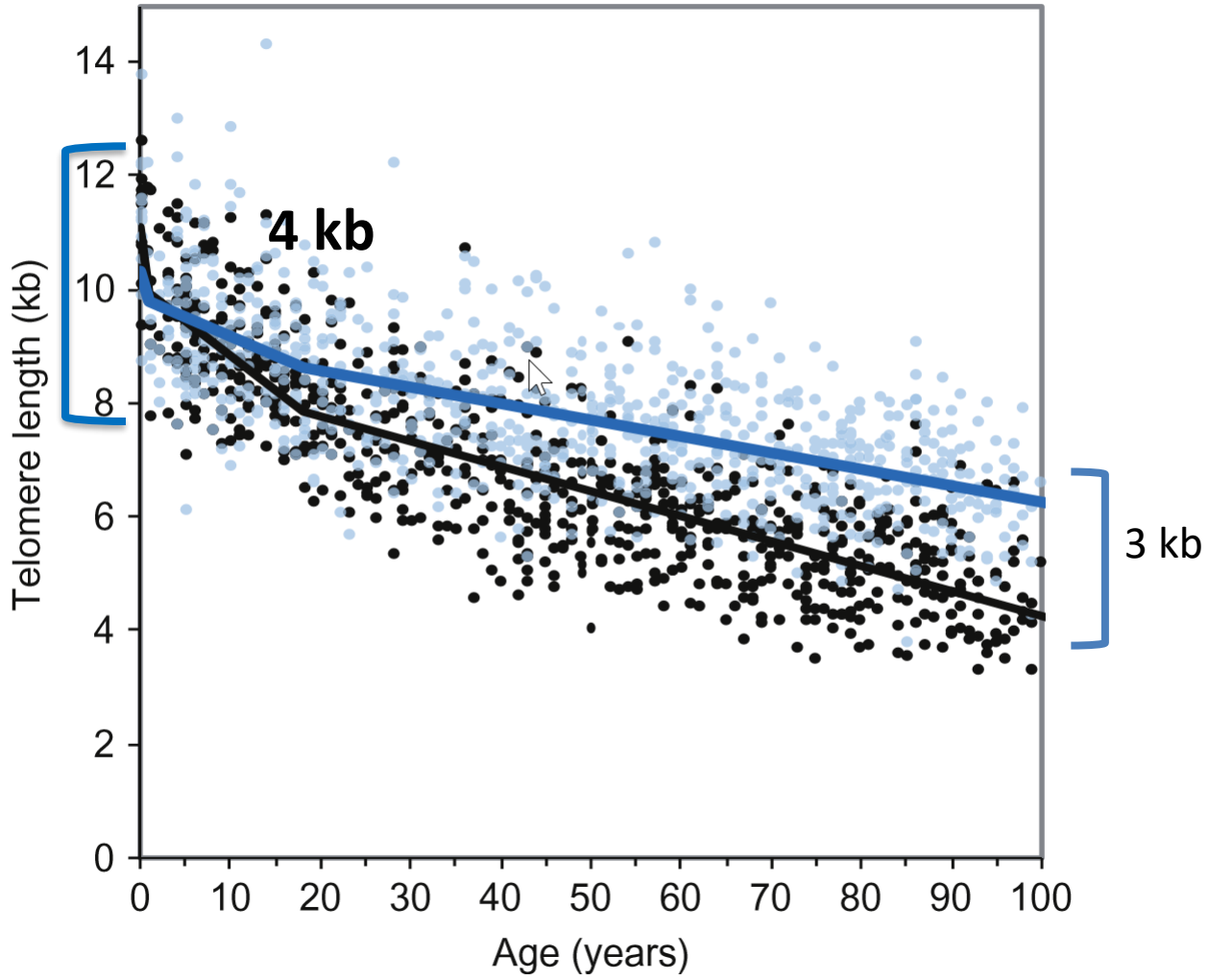
Shelterin Complex



Adapted from Neumann AA *Nature Reviews Cancer* **2** , 879-884

Telomeres: Length and Shortening with Age

- **Length: 10 kb (8-12 kb) at birth**
  - **Accelerated loss with growth**
  - **8 kb at young adulthood (4 kb variation)**
- **Aging: lose 0.05 kb per year**
  - **Critical TL ≈ 5 kb at end of life**
  - **8-5 kb = 3 kb avg loss over adult lifetime**
  - **Cell division**:
    - **Lose 100 base-pairs per division**
    - Mostly in stem cells and highly proliferative tissues (BM, WBC, gut, skin, etc.)
  - **Oxidative stress**:
    - **Increases loss with each division**
    - GGG portion of TTAGGG repeat very susceptible to free radicals
  - **End-replication problem**:
    - **Need telomerase**



Aubert G 2014 *Prog Mol Biol Trans Sci* vol 125

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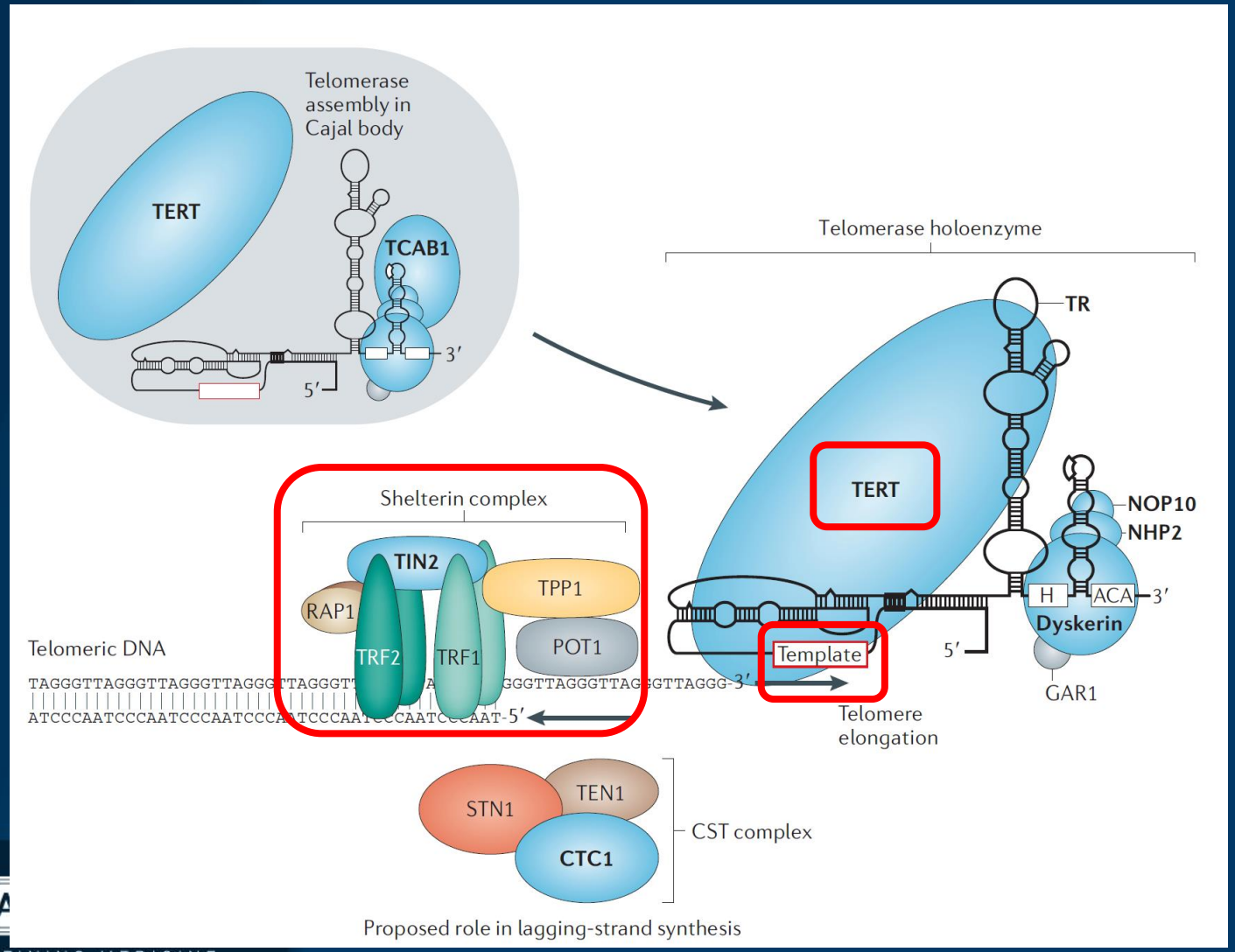
Telomerase Enzyme and Shelterin Complexes



Structure: Two components

- **hTERT**: **h**uman **te**lomerase **r**everse **t**ranscriptase, the catalytic component
- **TERC**: **te**lomerase **R**NA template **c**omponent (aka **TR**)

Function: Lengthen telomeres

Shelterin: Assembly of telomere binding proteins

Activation:

- Very active during embryogenesis
- Repressed before birth
- Repressed during adult life
- in most tissues except those with rapid turnover.
- ***Adult activity insufficient to maintain telomere length***

- ***Birth marks beginning of telomere erosion***

Reactivation:

- hTERT gene transduction
- Small molecule hTERT transcription activators

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Armanios M, Blackburn EH. Nature Reviews Genetics, 2012:13:693-704

Telomere Length Determinants

Inherited Length

- "Telotype": inherited trait
- Heritability rate 36-84% (Eisenberg D 2012)
  - Largest meta-analysis **70%**
  - Maternal > Paternal (Boer L 2013)
- Race: African > Caucasian
- Gender: female > male
- Paternal age is factor: Older men pass on longer telomeres (De Meyer T 2007)

Attrition Rate

- Slowing/reversing:
  - Telomerase activity
- Increasing:
  - Proliferative activity
    - Tissue injury, chronic infections and diseases
  - Oxidative stress
    - Smoking, obesity, sedentary lifestyle, hypertension, stress, low antioxidant status
- Heritability of attrition: 28% (Hjelmborg J et al *J Med Genet* 2015)

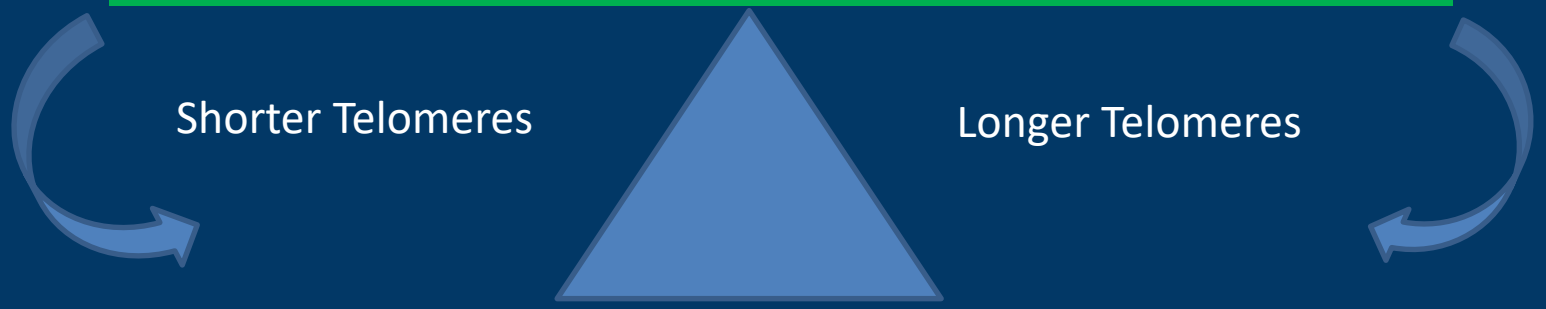
Telomere Attrition determined by balance between loss and telomerase activity

Tissue injury
Infections
Toxins
Stress

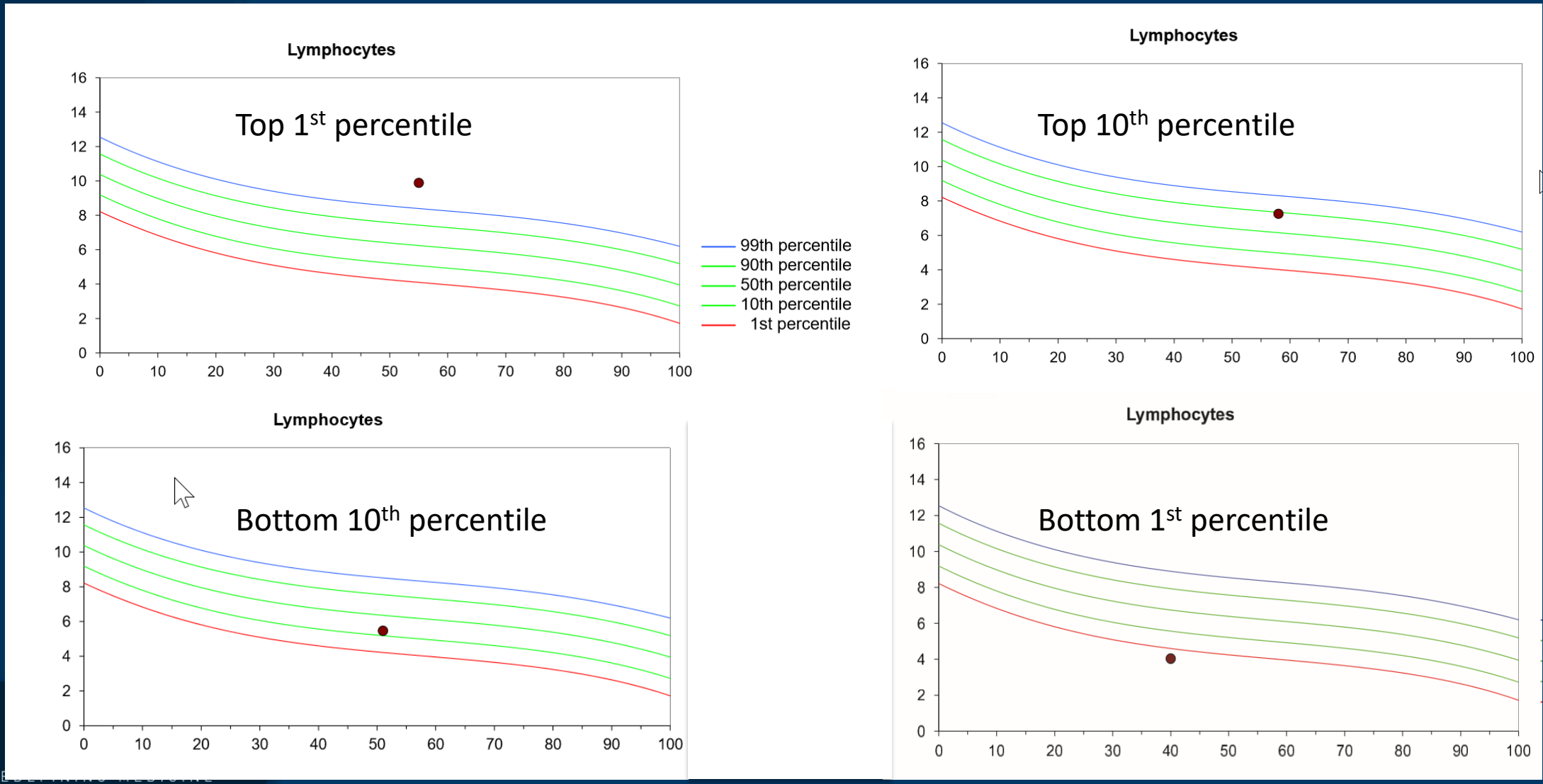
- Proliferative activity
- Oxidative stress
- Inflammation

Telomerase activity

Lifestyle
Diet
Stress control
Supplements
Meds



Telomere Length Variation: Does it Matter?



Telomeres: The New Cholesterol?

TELOMERES: THE NEXT CHOLESTEROL

If you haven't already, you will be hearing a lot in the coming years about telomeres—a part of our cellular anatomy that holds dramatic new information about the trajectory of our health and may turn out to provide the single most important biomarker of aging.

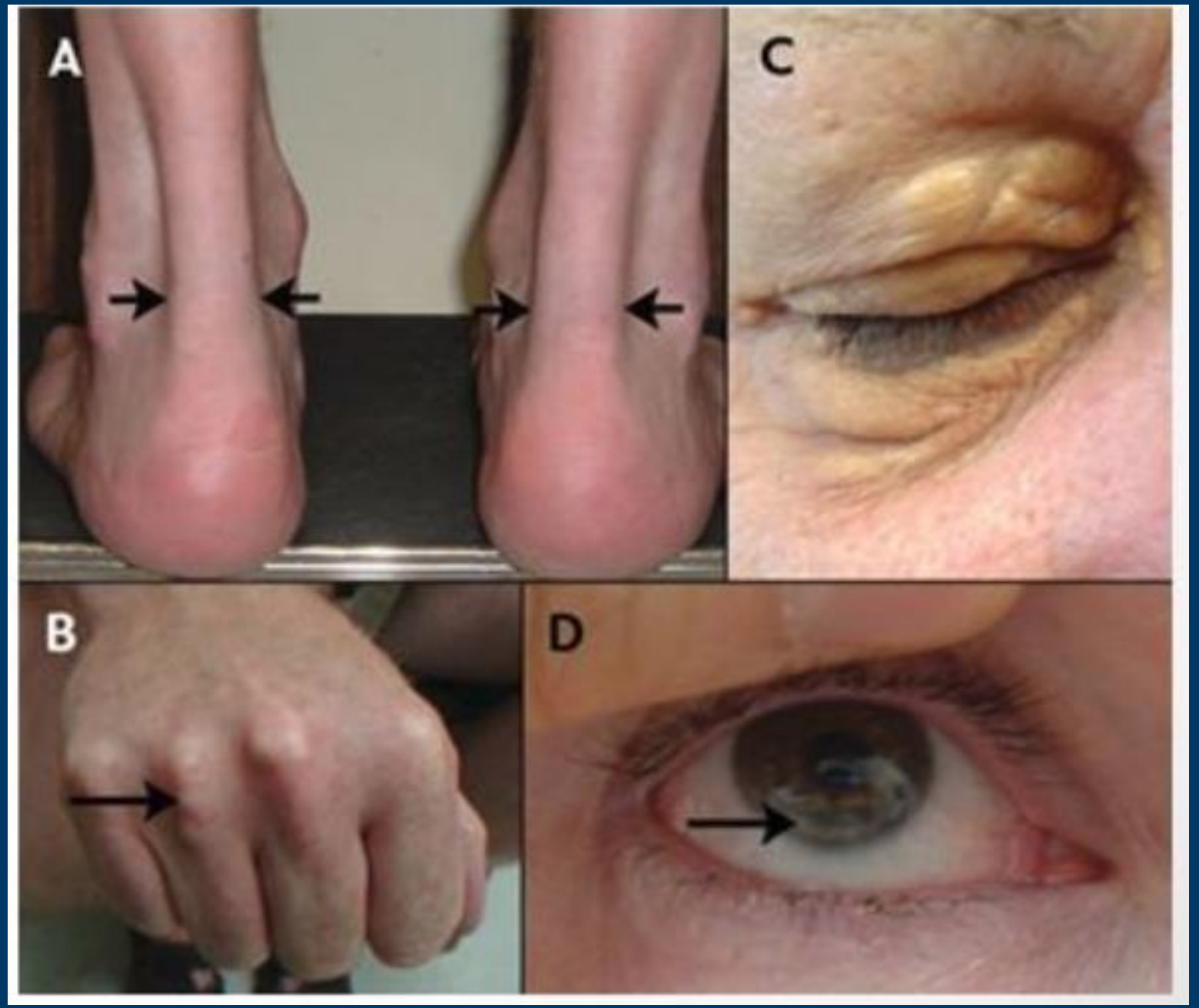
Drraffaele.com 2011

"While the aging process is complex and certainly cannot be explained solely on the basis of telomere biology, there is a growing consensus that in some situations telomere biology and telomere tests may have important utility similar to cholesterol assays or blood pressure monitoring measurements."

Jerry Shay, PhD 2012 Aging and the Telomere Connection

Genes load the gun. Lifestyle pulls the trigger.

Surface manifestations of Familial hypercholesterolemia



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Yuan G, Wang J, Hegele RA. CMAJ 2006;174:1124-9

Extreme cases in medicine inform more common milder dysfunction

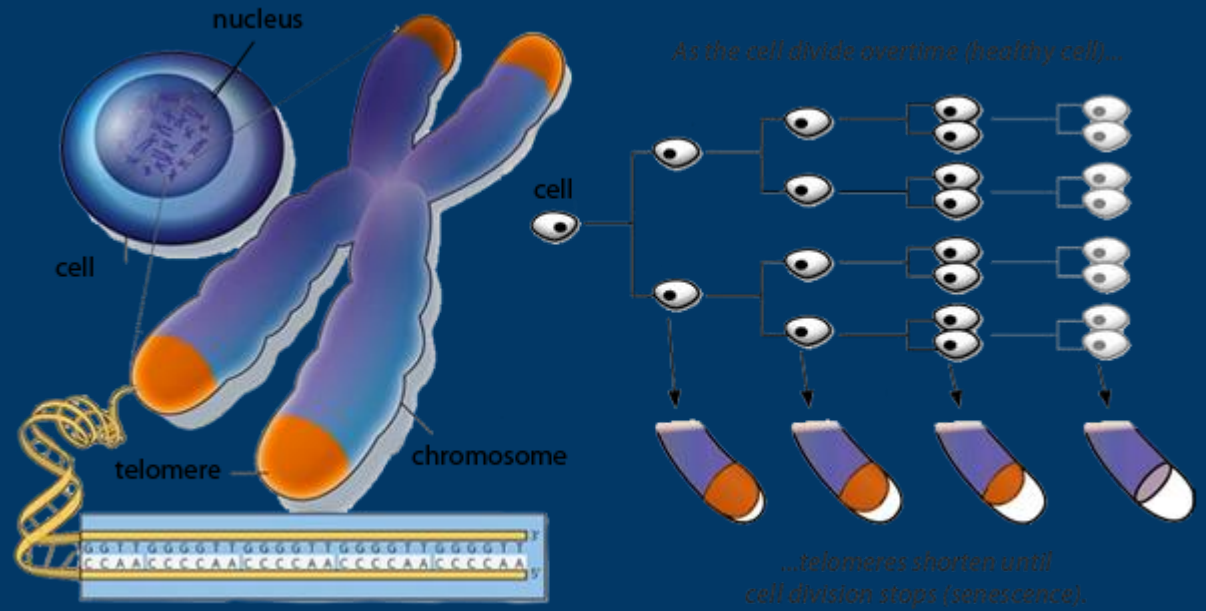
Genetic disorder

- **Familial hypercholesterolemia**
  - Monogenic: one of 4 genes
  - 1:500 prevalence (heterozygote)
  - 1:1,000,000 (homozygote)
  - High circulating cholesterol with deposition in tendons, skin, and coronary arteries causing premature MI
    - Heterozygous MI in 40-50s
    - Homozygous MI in 20s

Milder multifactorial disorder

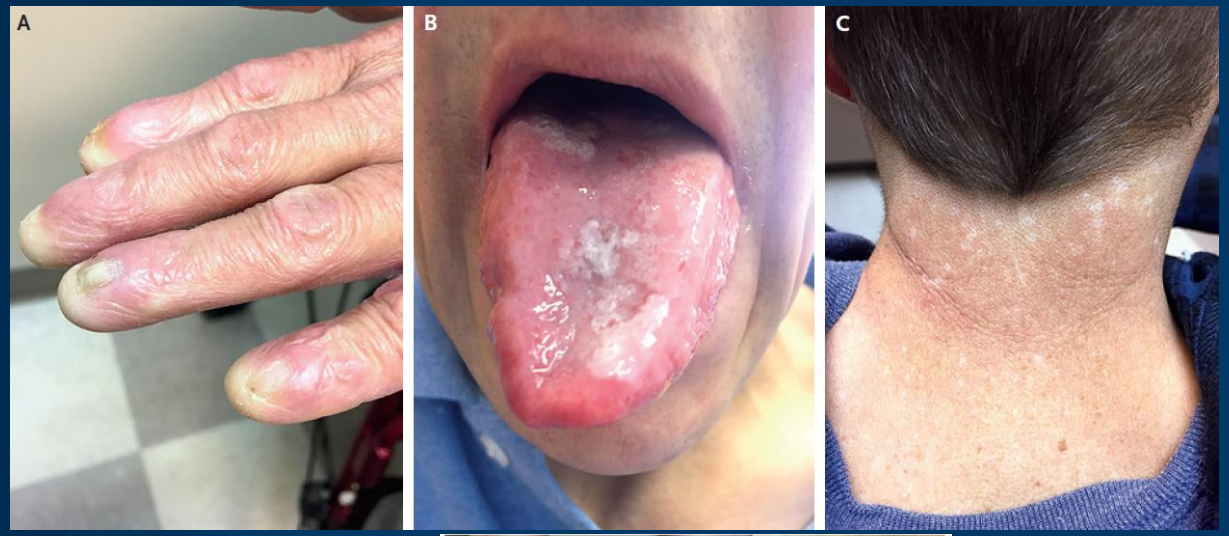
- **Hyperlipidemia**
  - 1:3 prevalence
  - Polygenic *plus* lifestyle/diet
  - High circulating cholesterol leads to atherosclerosis, MI, stroke, PAD
    - MI at 60 and older

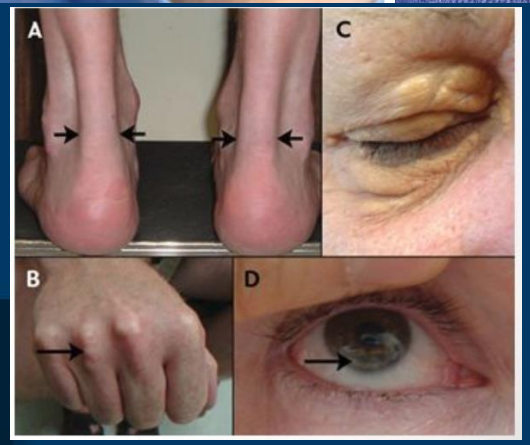
HUMAN SEVERE TELOMERE BIOLOGY DISORDERS (TBD)



Proof that telomere length matters!

First Primary TBD: Dyskeratosis Congenita Clinical Manifestations





- **Rare childhood disorder**
- **High turnover tissues**
  - Deformed nails
  - Tongue white patches
  - Irregular pigmentation

  } Triad of surface manifestations
  - **Aplastic anemia**, BM failure
    - 80% Die of it by age 30
  - 10% get cancer
    - Head/neck
    - Leukemias
  - Intestinal epithelial abnormalities
- **Slow turnover tissues**
  - **Pulmonary fibrosis**
  - Cirrhosis
  - Impaired glucose tolerance
  - Insulin resistance
  - osteoporosis

Kelmenson DA *N Engl J Med* 2017

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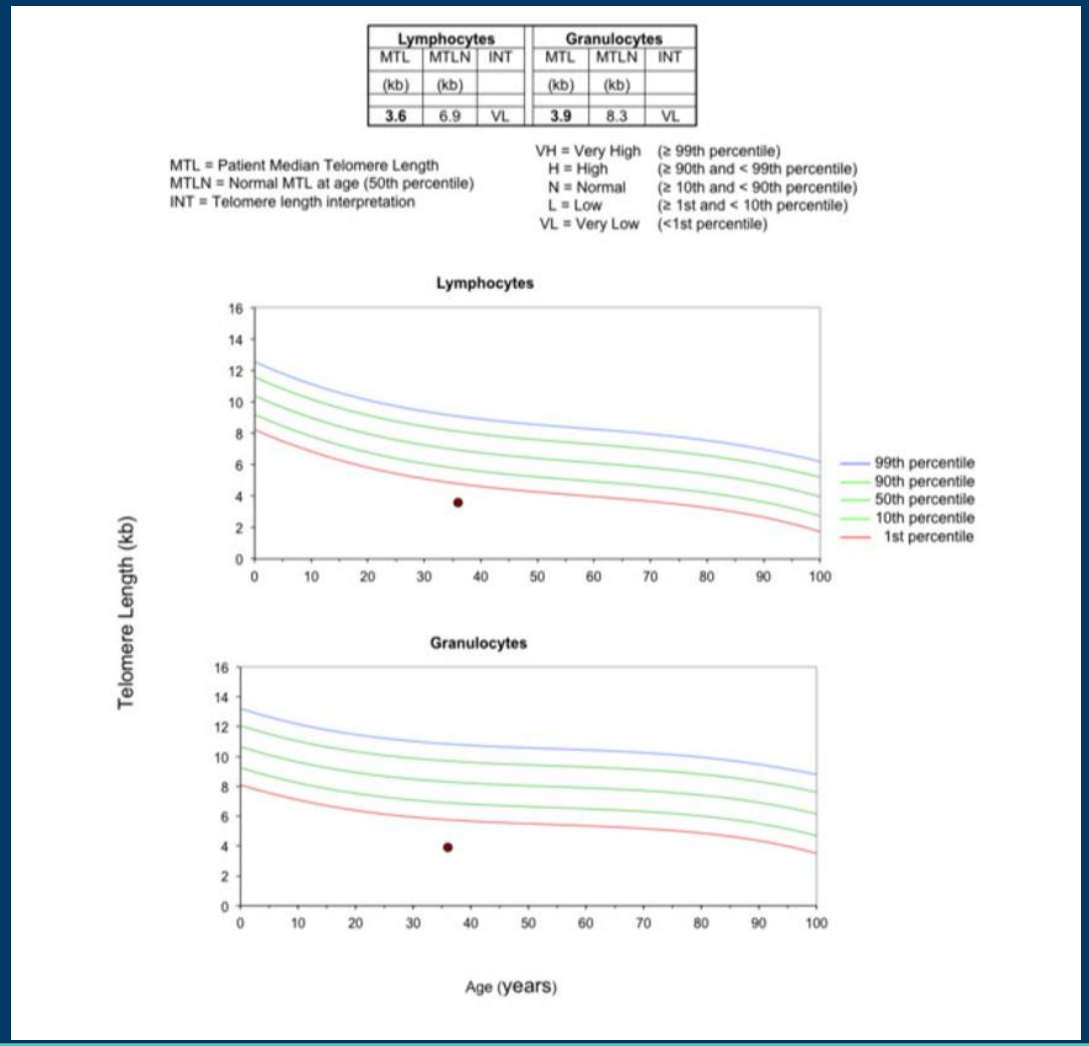
DKC: Disease of very short telomeres



Lymphocytes			Granulocytes		
MTL (kb)	MTLN (kb)	INT	MTL (kb)	MTLN (kb)	INT
3.6	6.9	VL	**3.9**	8.3	VL

MTL = Patient Median Telomere Length
MTLN = Normal MTL at age (50th percentile)
INT = Telomere length interpretation

VH = Very High (≥ 99th percentile)
H = High (≥ 90th and < 99th percentile)
N = Normal (≥ 10th and < 90th percentile)
L = Low (≥ 1st and < 10th percentile)
VL = Very Low (<1st percentile)

- **< 10th percentile** telomere length
- **< 1st percentile is 95% *sensitive* and *specific*** for a telomeropathy

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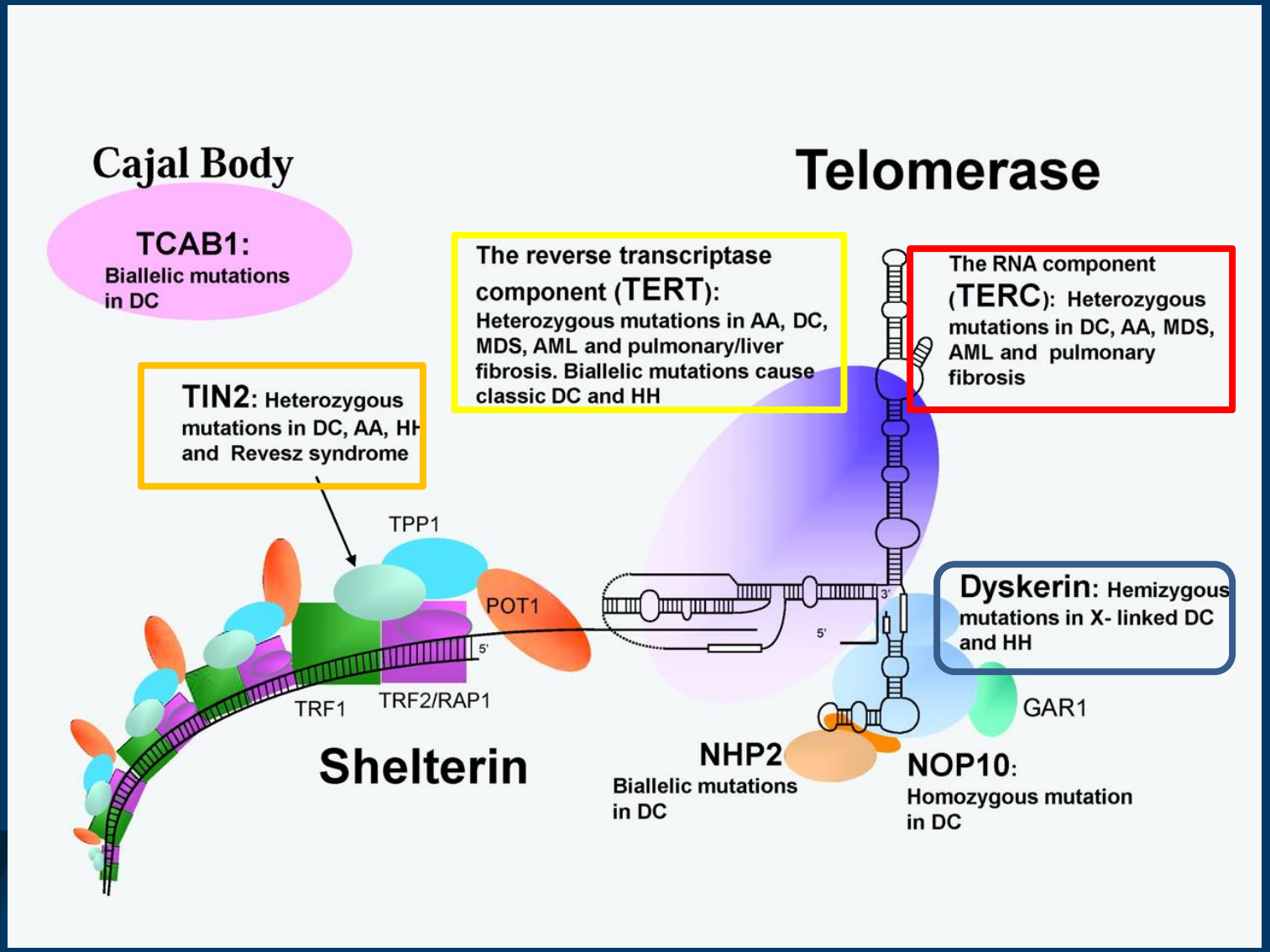
Mutations in Telomere Biology Disorders

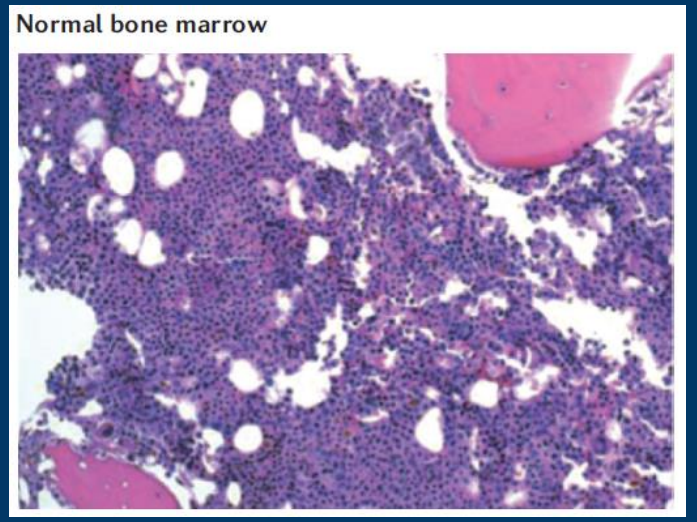
- Dyskeratosis Congenita
- Aplastic Anemia
- Pulmonary Fibrosis

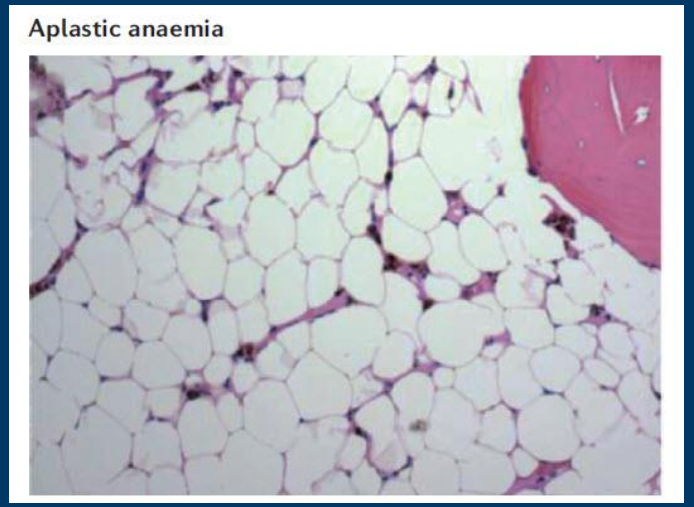


Adapted from Dokal I Hematology 2011;2011:480-486

Idiopathic Aplastic Anemia

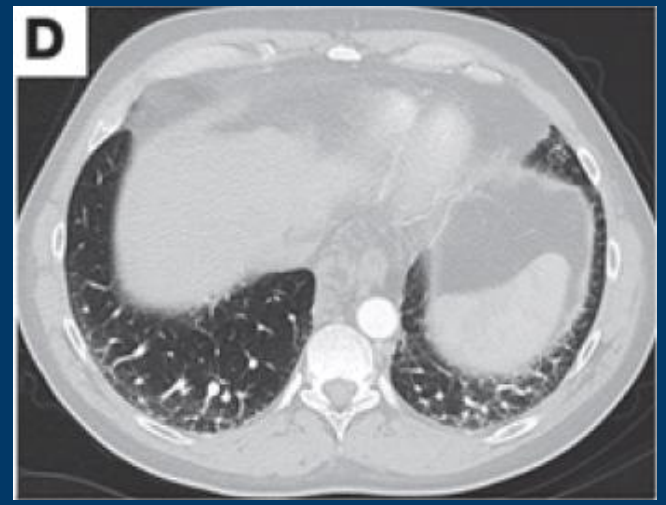
- **Aplastic anemia (AA):**
  - Acquired AA is immune mediated, infectious, or environmental
  - **Inherited bone marrow failure often presents as isolated AA**
    - 10% with isolated AA have autosomal dominant (AD) mutations of TERT and TERC.
    - Telomere length is below 10th percentile for age
    - Presents in 20s to 40s
    - **50% telomerase activity**





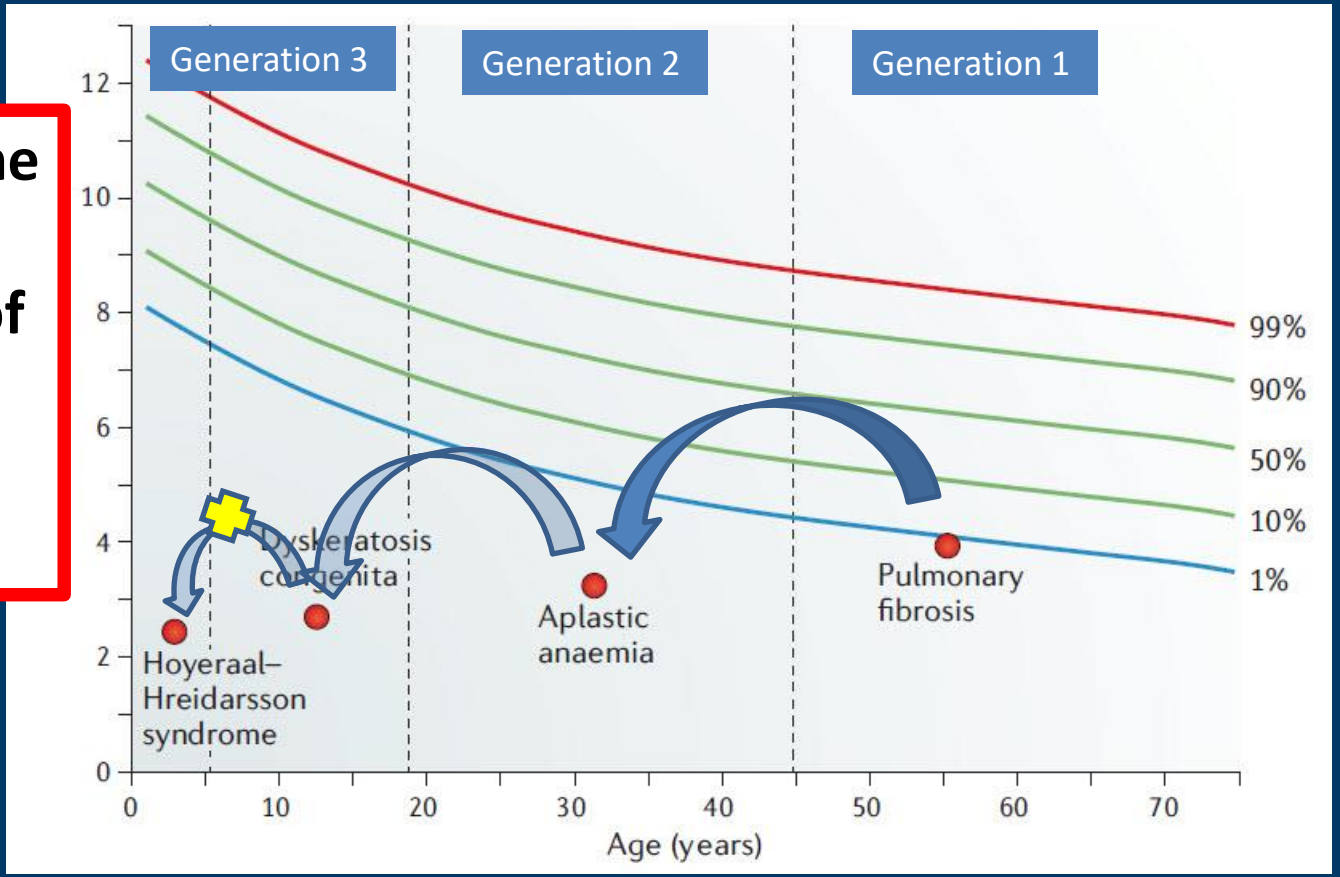
Idiopathic Pulmonary Fibrosis (IPF)

- Progressive, generally fatal, disease of the lungs causing scarring and loss of alveolar airspace
- Prevalence (US): 128,000
  - Incidence: 48,000
  - Mean age diagnosis: 51 years old
  - Mortality per year: 40,000
- 1-3% of cases w/ TERT or TERC mutations
- **Most prevalent manifestation of a TBD**
- **Latest presentation of a TBD**
- **50% telomerase activity**



Genetic Anticipation of Age of Onset and Clinical Manifestations

Telomere length **is the determinant of the onset and severity of disease, not *telomerase activity***



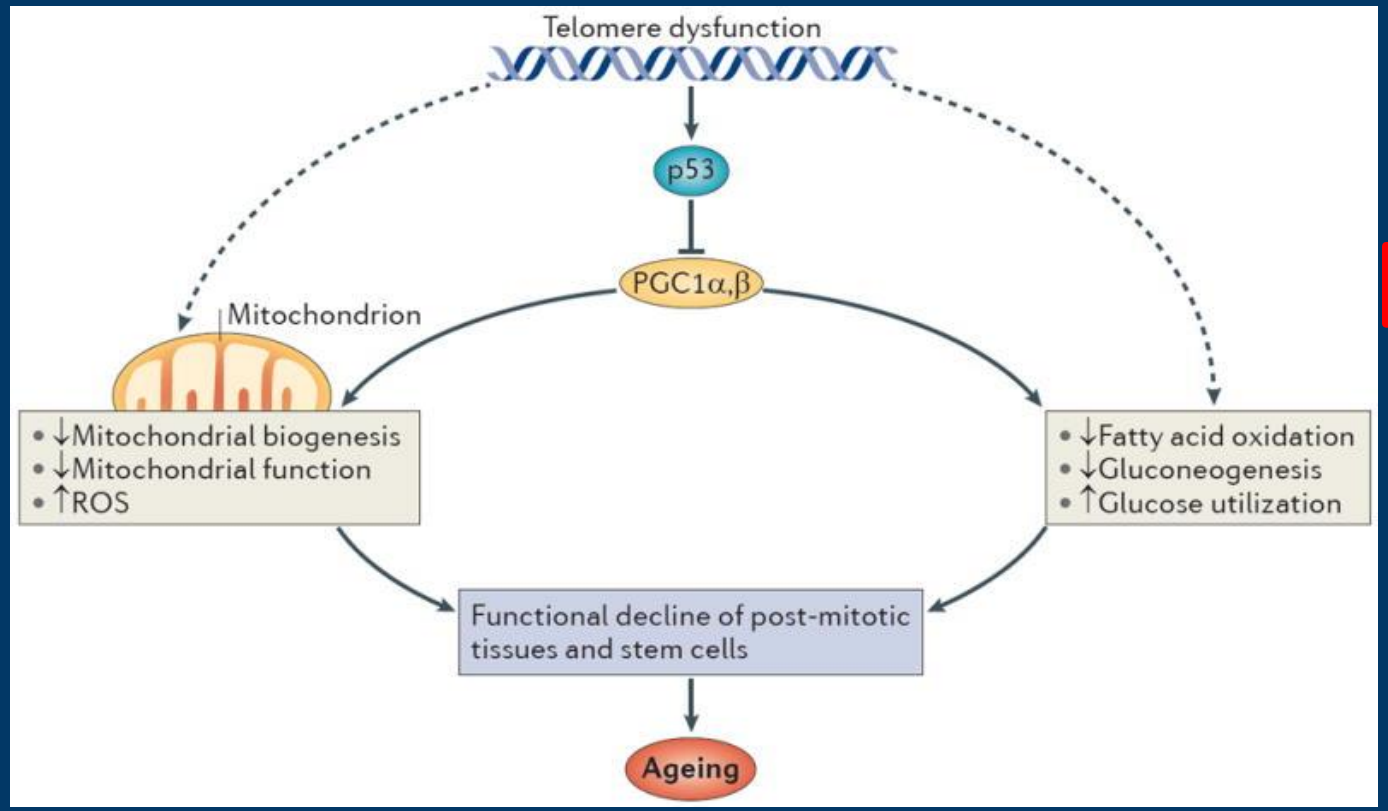
Progressively shorter telomere length inherited with each generation

Adapted from Armanios, M, Blackburn EH. The Telomere Syndromes, Nature Reviews Genetics, 2012:13:693-704

How Are Slow Turnover Tissues Affected by Short Telomeres?

Telomere Mitochondria connection: PGC1α,β

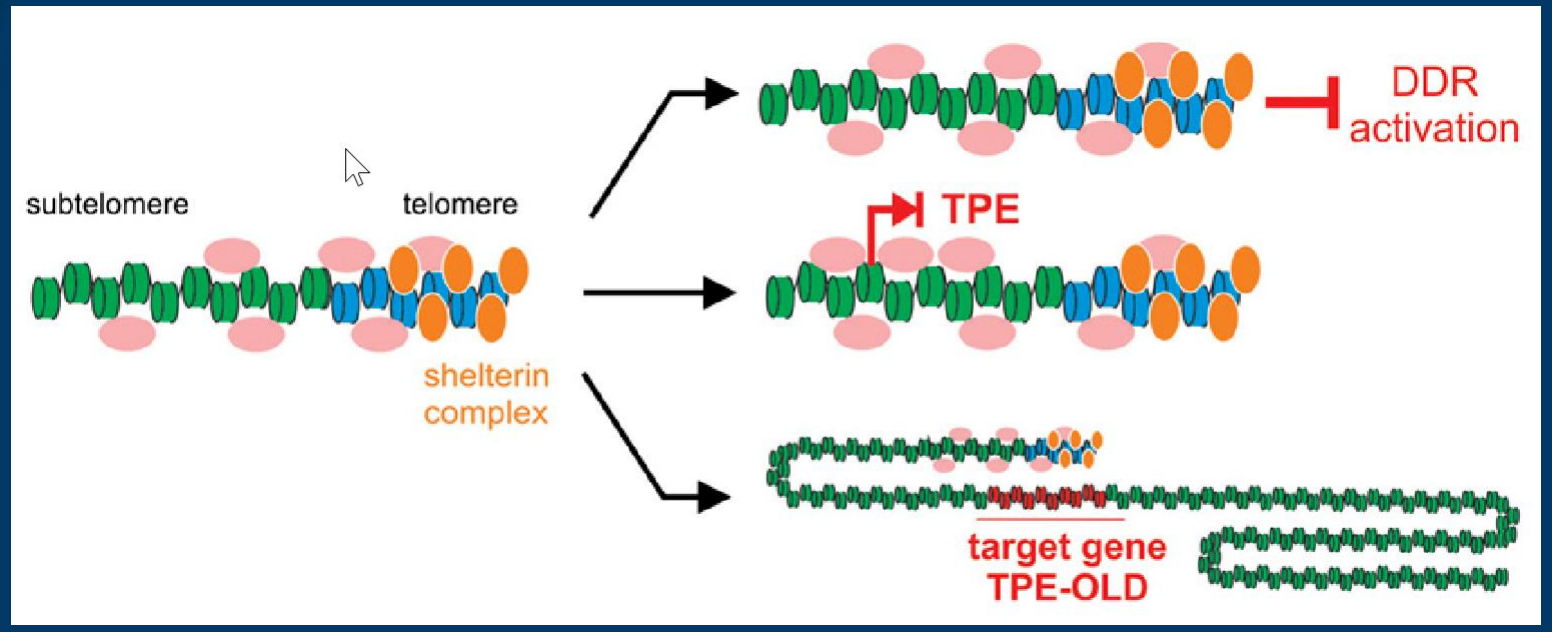
↓ Mitochondria number



↓ Mitochondria efficiency

Sahin E 2012 *Nat Rev Mol Cell*

Telomere Position Effect

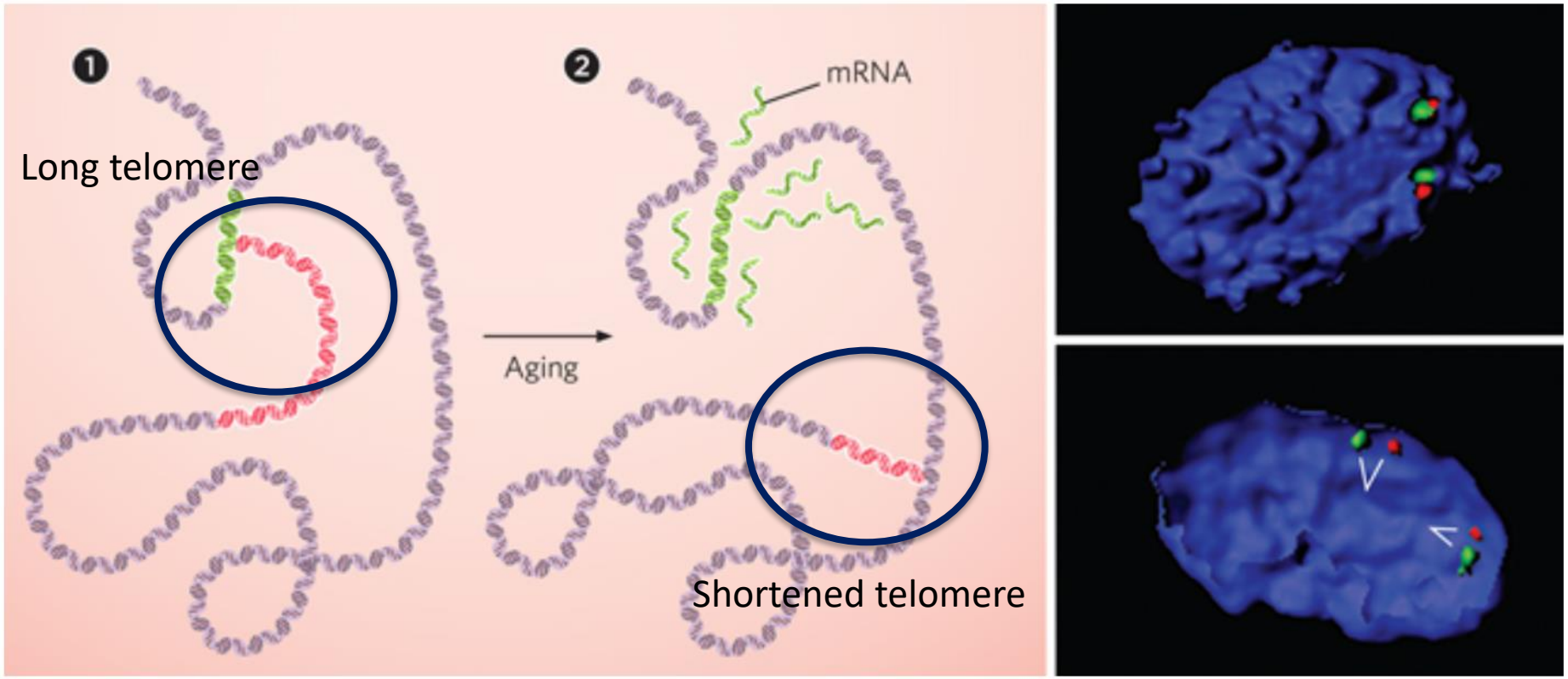


Classic TPE, spreading heterochromatin suppresses genes next to telomere

Over **L**ong **D**istances by looping of chromatin
Regulates genes up to 10Mb away

"A final, particularly interesting question that arises from these studies is whether the effects on distal genes occur prior to telomeres reaching the threshold below which senescence pathways are activated. **If so, telomeres would be not only guardians of the genome but also its regulators**."

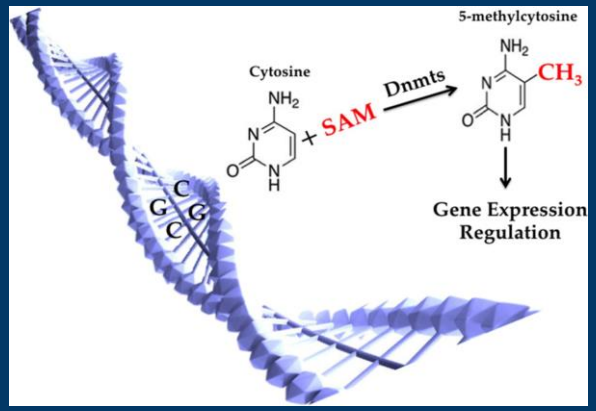
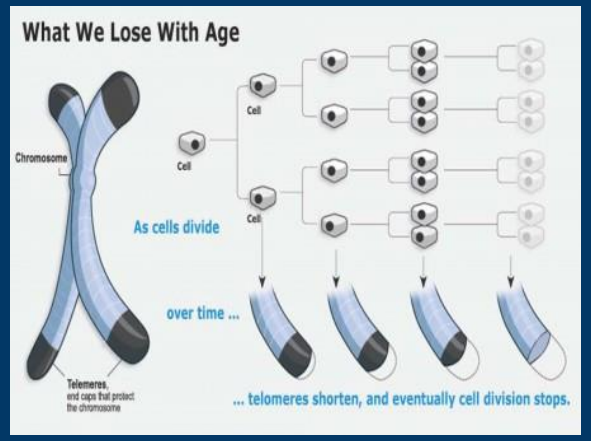
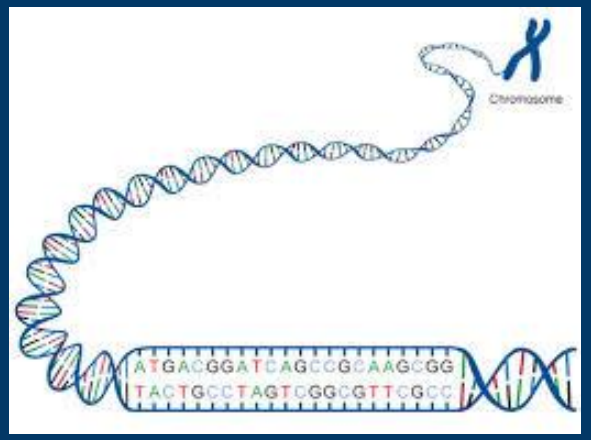
Misteli T. The long reach of telomeres. Genes Dev. 2014 Nov 15;28(22):2445–6.



REGULATORY ROLE: Early in life, when telomeres (red) are long, chromosome looping brings them into contact with particular genes (green) (1). As cells age, their telomeres shorten. Through mechanisms that are not yet understood, this alters chromosome looping and telomeres' interactions with genes, leading to age-related changes in gene expression (2). Imaging using 3D-FISH (right panels) illustrates the distance between a certain gene and long (top) and short (bottom) telomeres.

ILLUSTRATION © STEVE GRAEPEL; IMAGES COURTESY OF JERRY SHAY

https://www.the-scientist.com/the-literature/rethinking-telomeres-35860

Level of Phenotype Control		Type of DNA	Heritability
Epigenetics **Expression**		**Not DNA**: CpG Methylation, Histones, Etc.	Partially Heritable? Highly modifiable
Telo-genetics **Length**		**Non-coding DNA** TTAGGG length important	Highly Heritable/ Partially modifiable
Genetics **Sequence**		**Coding DNA**	100 percent Heritable/ Not modifiable CRISPR?

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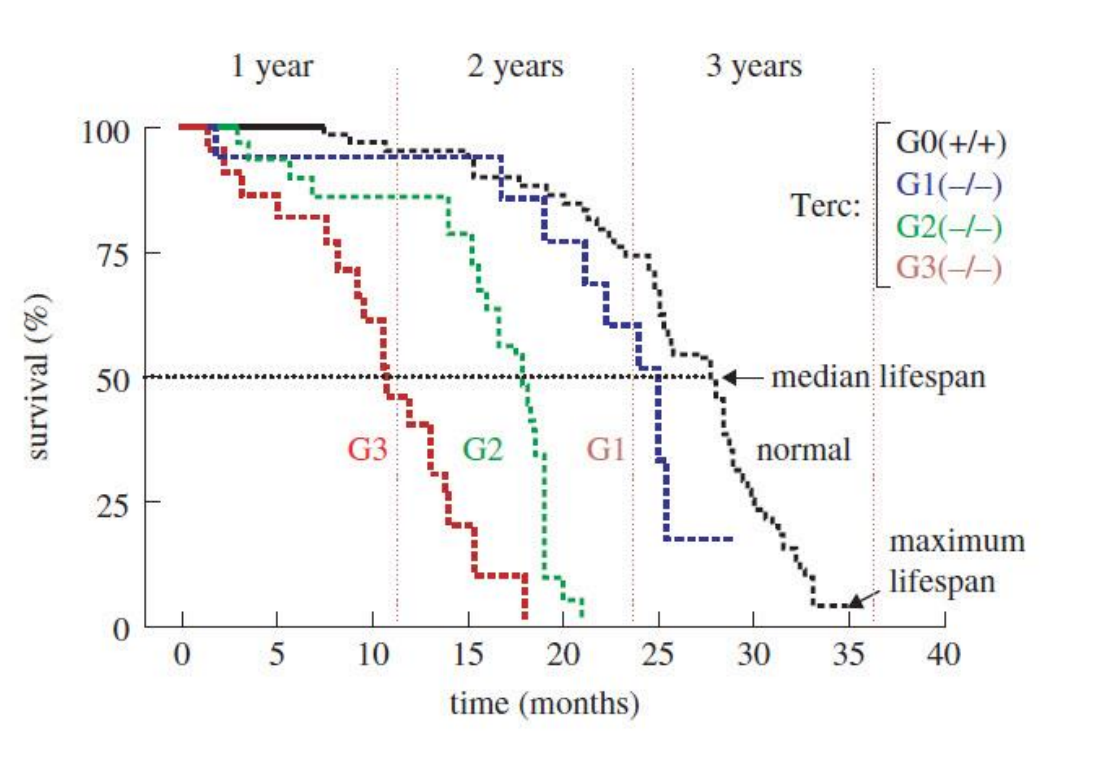
Telomeres are not just a molecular clock

- Regulate mitochondrial function/biogenesis
- Regulate gene expression

Telomeres and Knockout Mouse Models

- **Normal lab mice (*mus musculus*)**
  - Have long telomeres (50-70 kb), humans 6-12 kb
- **Don't exhibit typical human aging**
  - Some degenerative disease but most die of cancer,
  - Not of epithelial cells, but sarcomas/lymphomas
- **Telomerase knockout (KO)**
  - With complete telomerase knockout
  - Mice shorten telomeres over 3 generations

Telomerase KO Mice



- TERC -/- KO mice
- **Progessive decrease mean/max lifespan**
- Decreased telomere length
- Premature aging pathologies worse with each generation
- Genetic anticipation similar to telomeropathies
- But, mostly high turnover tissues
  - BM, gut, germ cells

Donate LE, Blasco MA. Telomeres in cancer and ageing. Philos Trans R Soc Lond, B, Biol Sci. 2011 Jan 12;366(1561):76–84.

First Age Reversal in a Mammal

Telomerase reactivation reverses tissue degeneration in aged telomerase-deficient mice

Mar
Mar

- Tel
  you
- 33
- Bra
- Re
- Se
- **No**

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Nature. 2011 Jan 6;469(7328):102–6.

Further Proof of Concept: Intervention

Telomerase gene therapy in adult and old mice delays aging and increases longevity without increasing cancer

AAV wide tropism expressing mouse TERT had remarkable beneficial effects on health and fitness, including insulin sensitivity, osteoporosis, neuromuscular coordination and several molecular biomarkers of aging

DOI 10.1002/emmm.201200245

Received February 22, 2012
Revised March 29, 2012
Accepted March 30, 2012

effects of a telomerase gene therapy in adult (1 year of age) and old (2 years of age) mice. Treatment of 1- and 2-year old mice with an adeno associated virus (AAV) of wide tropism expressing mouse TERT had remarkable beneficial effects on health and fitness, including insulin sensitivity, osteoporosis, neuromuscular coordination and several molecular biomarkers of aging. Importantly, telomer-

telomerase-treated mice, both at 1-year and at 2-year of age, had an increase in median lifespan of 24 and 13%, respectively.

telomerase activity. Together, these results constitute a proof-of-principle of a role of TERT in delaying physiological aging and extending longevity in normal mice through a telomerase-based treatment, and demonstrate the feasibility of anti-aging gene therapy.

→See accompanying article
http://dx.doi.org/10.1002/emmm.201200246

- Less DNA damage with aging
- Lower total and LDL cholesterol
- Improved glucose and insulin tolerance
- Enhanced mitochondrial function
- Lower cancer incidence
- Longer lifespans

nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-019-12664-x OPEN

Mice with hyper-long telomeres show less metabolic aging and longer lifespans

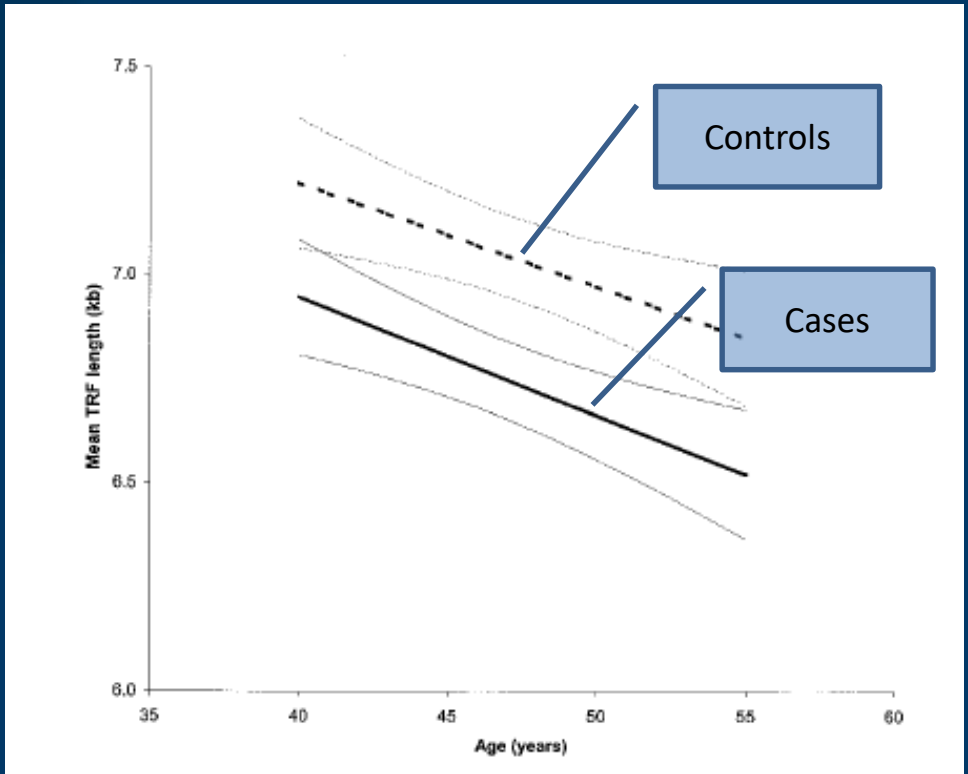
Miguel A. Muñoz-Lorente[1], Alba C. Cano-Martin[1] & Maria A. Blasco[1*]

Muñoz-Lorente MA, Cano-Martin AC, Blasco MA. Mice with hyper-long telomeres show less metabolic aging and longer lifespans. Nat Commun. 2019 Oct 17;10(1):1–14.

Telomeres and Common Disease Association

- **Chronic disease association**
  - Hypertension
  - Atherosclerosis
  - COPD
  - Alzheimer's dementia
  - Cancer
  - Obesity/Diabetes
  - Metabolic syndrome
  - Chronic stress
- **Mortality association**:
  - Cawthon 2003 *Lancet:* Landmark study in subjects 60 years old
    - Those with longest telomeres lived longer than shortest telomeres. Cause of death infection
  - Fitzpatrick 2011 *J Gerontol A Biol Sci Med Sci*: The Cardiovascular Health Study
    - Shortest quartile of telomere length 60% more likely to die than longest quartile. Cause again infectious

Telomere length sheds light on relationship between CVD risk factors and events



- Having shorter than average lymphocyte mean telomere length **increased the risk of premature MI roughly 3-fold**
- The difference in telomere length between cases and controls translates into **a biological age difference of 11 years**
- An example of telomere length as a modifier of disease onset

Brouilette S 2003 *Arterioscler Throm Vasc Biol*

Cardiovascular Disease

thebmj

BMJ 2014;349:g4227 doi: 10.1136/bmj.g4227 (Published 8 July 2014)

RESEARCH

Leucocyte telomere length and risk of cardiovascular disease: systematic review and meta-analysis

OPEN ACCESS

Philip C Haycock *postdoctoral research assistant*[1 2], Emma E Heydon *doctoral candidate*[1], Stephen Kaptoge *senior research associate*[1], Adam S Butterworth *university lecturer*[1], Alex Thompson *senior epidemiologist*[1 3], Peter Willeit *research associate*[1 4]

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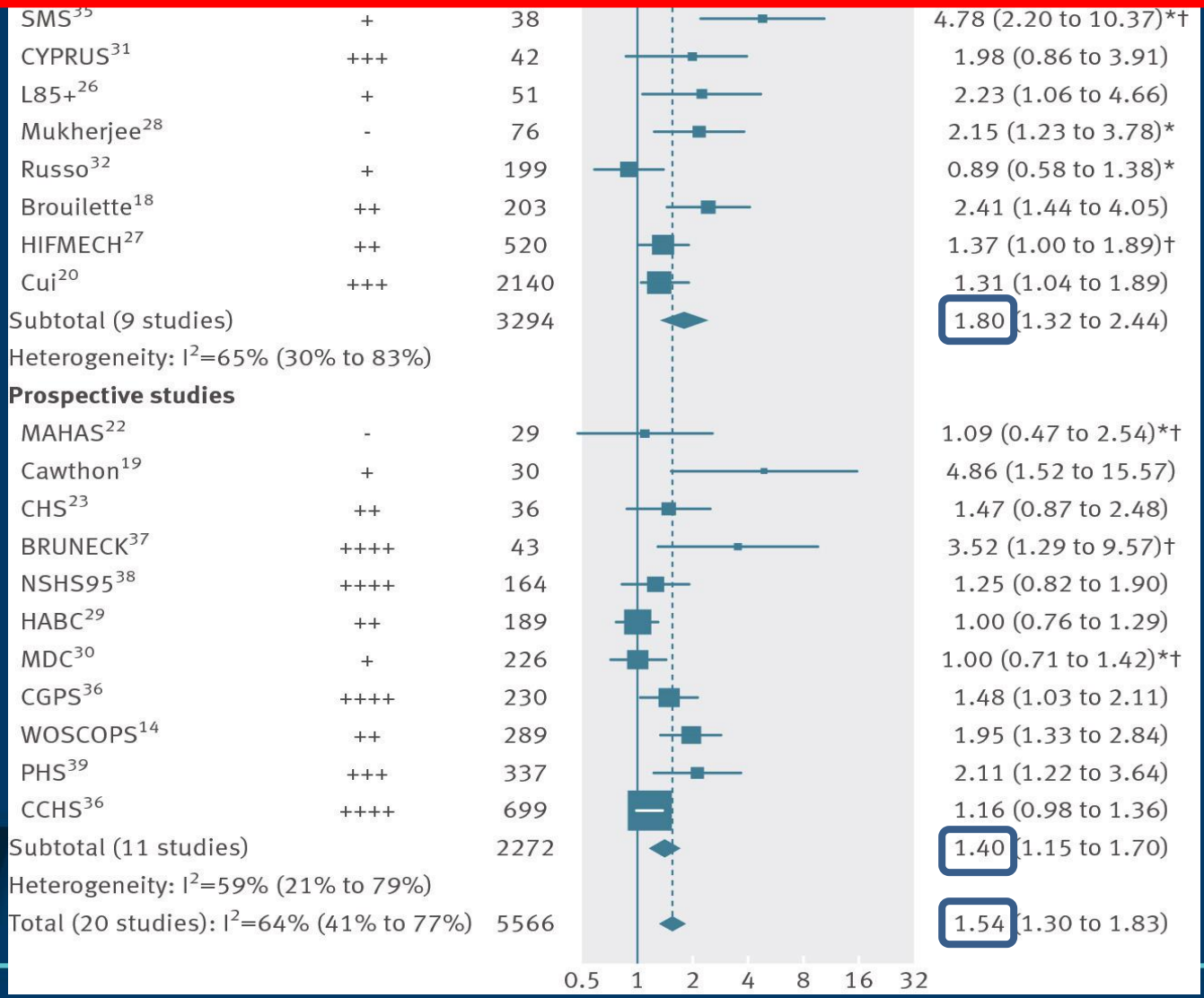
"This meta-analysis indicates that telomere length is inversely associated with risk of coronary heart disease independently of conventional vascular risk factors."



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Peripheral Blood Leukocyte Telomere Length and Mortality Among 64,637 Individuals From the General Population

- Copenhagen
- 42-70 years old
- 0-22 years follow up (7 yr mean)
- qPCR TL decile comparison
- 3 SNP genetic risk score

7607 Deaths

CVD — 2633

Cancer — 2420

HR = 1.4 for 10th v 1st decile and similar for CVD and cancer

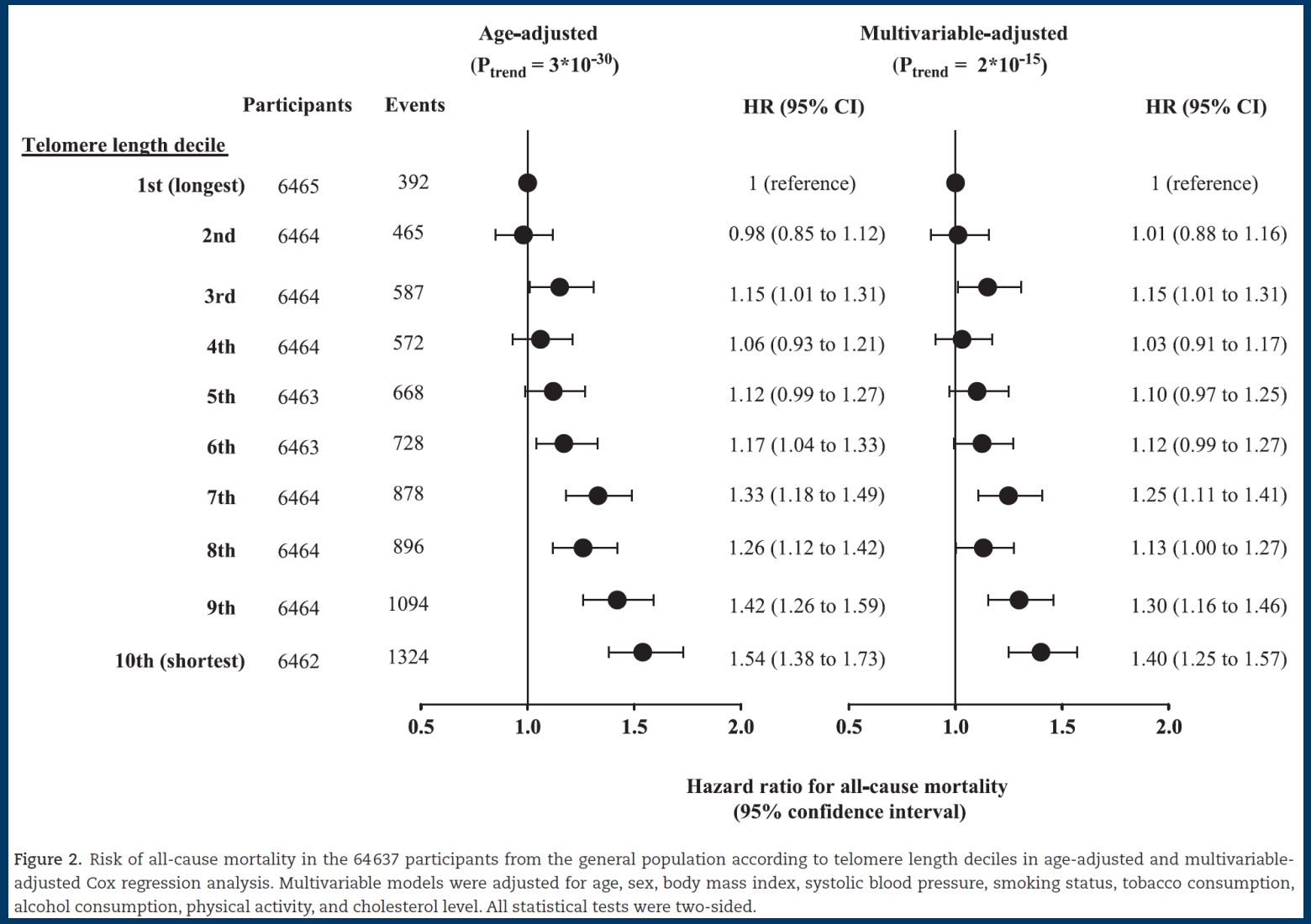

Figure 2. Risk of all-cause mortality in the 64637 participants from the general population according to telomere length deciles in age-adjusted and multivariable-adjusted Cox regression analysis. Multivariable models were adjusted for age, sex, body mass index, systolic blood pressure, smoking status, tobacco consumption, alcohol consumption, physical activity, and cholesterol level. All statistical tests were two-sided.

Rode L J Natl Cancer Inst. 2015;107(6)

Effective Telomere Length Enhancers?

- **Lifestyle**
  - Stress reduction Epel ES 2004 *PNAS*
  - Weight loss Valdez AM 2005 *Lancet*
  - Smoking cessation Song Z 2010 *Aging Cell*
- **Exercise** Ludlow A 2011 *J Aging Res*
  - Mitigates effect of perceived stress Puterman E 2010 *PloS One*
- **Diet**
  - Omega-3 intake Farzaneh-Far R 2010 *JAMA*
  - Low fat intake Ornish D 2008 *Lancet Oncol*
- **Supplements**
  - Vitamin D Richards BJ 2007 *Am J Clin Nutr*
  - Antioxidants Paul L 2011 *J Nutr Biochem*
  - Astragalus root extract (TA-65) Harley CB 2011 *Rejuvenation Res*
- **Hormones**
  - HRT increases telomerase activation (TA) Calado RT 2009 *Blood*
  - Cortisol decreases TA Choi J 2008 *Brain Behav Immun*
  - Growth hormone increases TA Moverare-Skrtic S 2009 *JCEM*

Effect of TA-65® on Telomere Length in Humans

- Study was conducted in Barcelona, Spain.
- Randomized, double-blind, placebo controlled study; Men and Women (50-84 years old); N=97
- Clinic visit at every 3 months with telomere length testing and routine blood tests

TA-65® Group
Increase in median telomere length

Time (months)	Increase in length (base pairs)
3 months	+384 (± 195) bp *
6 months	+158 (± 164) bp
9 months	+526 (± 167) bp *
12 months	+533 (± 183) bp *

Placebo Group
Decrease in median telomere length

Time (months)	Decrease in length (base pairs)
3 months	-24 (± 106) bp
6 months	none
9 months	-170 (± 106) bp *
12 months	-288 (± 101) bp *

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* Statistically significant

Salvador L, Singaravelu G, Harley CB, Flom P, Suram A, Raffaele JM. A Natural Product Telomerase Activator Lengthens Telomeres in Humans: A Randomized, Double Blind, and Placebo Controlled Study. Rejuvenation Res. 2016 Dec;19(6):478–84.

Telomerase Activation and Coronary Heart Disease
The TACTIC Trial

Secondary Prevention

Primary Objective

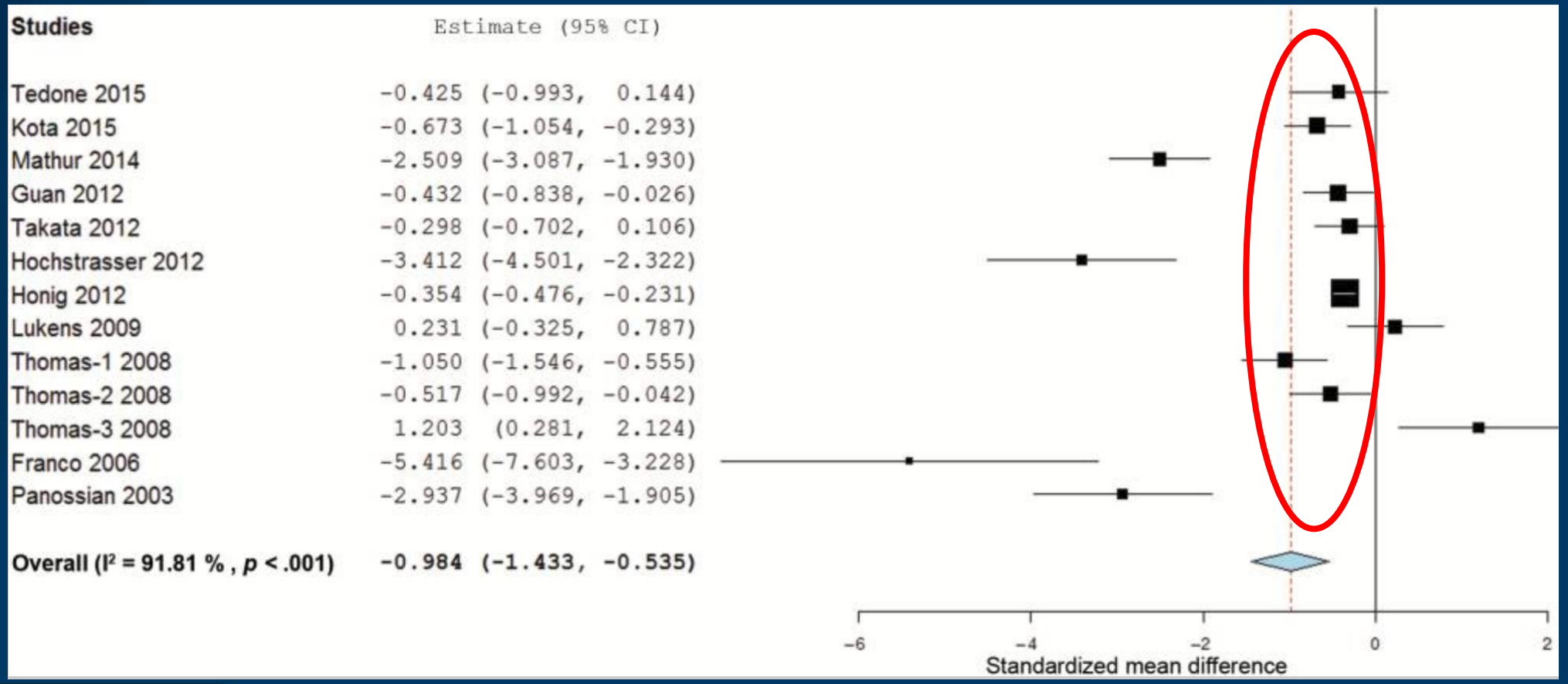
- Subjects ≥ 65 y.o. with treated ACS in the previous 6 months and documented CHD by angiography
- Assess the effect of 1-year TA-65® treatment on immunosenescence (terminally differentiated CD8+ T-cells—TEMRA) in older patients following acute coronary syndrome (ACS)

Secondary Objectives

- Telomere length and telomerase activity
- Endothelial function: EndoPat
- Inflammation: NT-proBNP and hsCRP
- Oxidative stress
- Clinical events: Death, stroke, and MI
- Effect of CMV seropositivity on outcomes

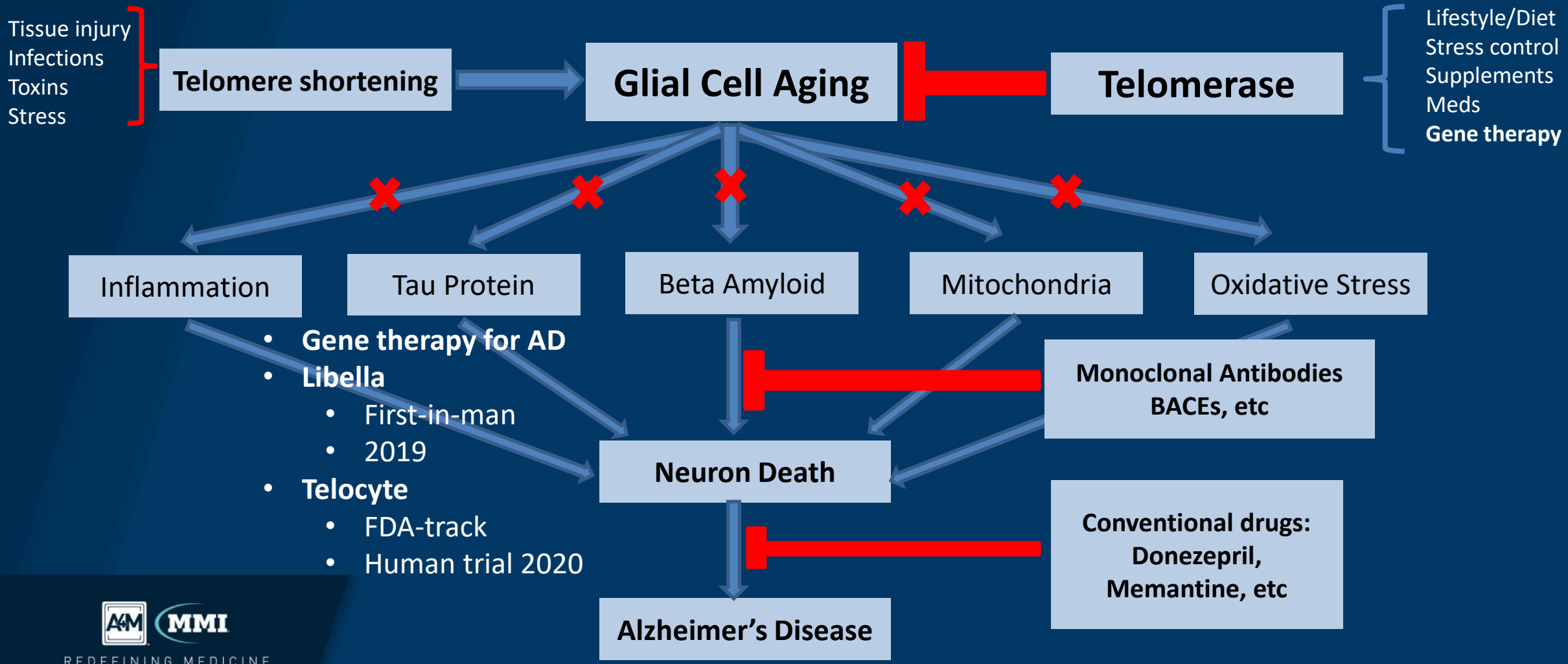
https://www.ukctg.nihr.ac.uk/trials

Telomere Length and Alzheimer's Dementia



Forero DA et al. Meta-analysis of Telomere Length in Alzheimer's Disease. J Gerontol A Biol Sci Med Sci. 2016 Aug;71(8):1069–73.

Telomere Theory of AD Intervention



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Aging Cell Open Access ANATOMICAL SOCIETY

Aging Cell. 2019 Aug; 18(4): e12979.
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PMCID: PMC6612639
PMID: 31152494

Transient introduction of human telomerase mRNA improves hallmarks of progeria cells

Yanhui Li, [1] Gang Zhou, [2] Ivone G. Bruno, [3] Ning Zhang, [1] Sei Sho, [1] Enzo Tedone, [1] Tsung-Po Lai, [1] John P. Cooke, [2] and Jerry W. Shay [1]

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frontiers in Genetics

REVIEW
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Are There Common Mechanisms Between the Hutchinson–Gilford Progeria Syndrome and Natural Aging?

Vasily V. Ashapkin, Lyudmila I. Kutueva, Svetlana Y. Kurchashova and Igor I. Kireev*

Belozersky Research Institute of Physico-Chemical Biology, Lomonosov Moscow State University, Moscow, Russia

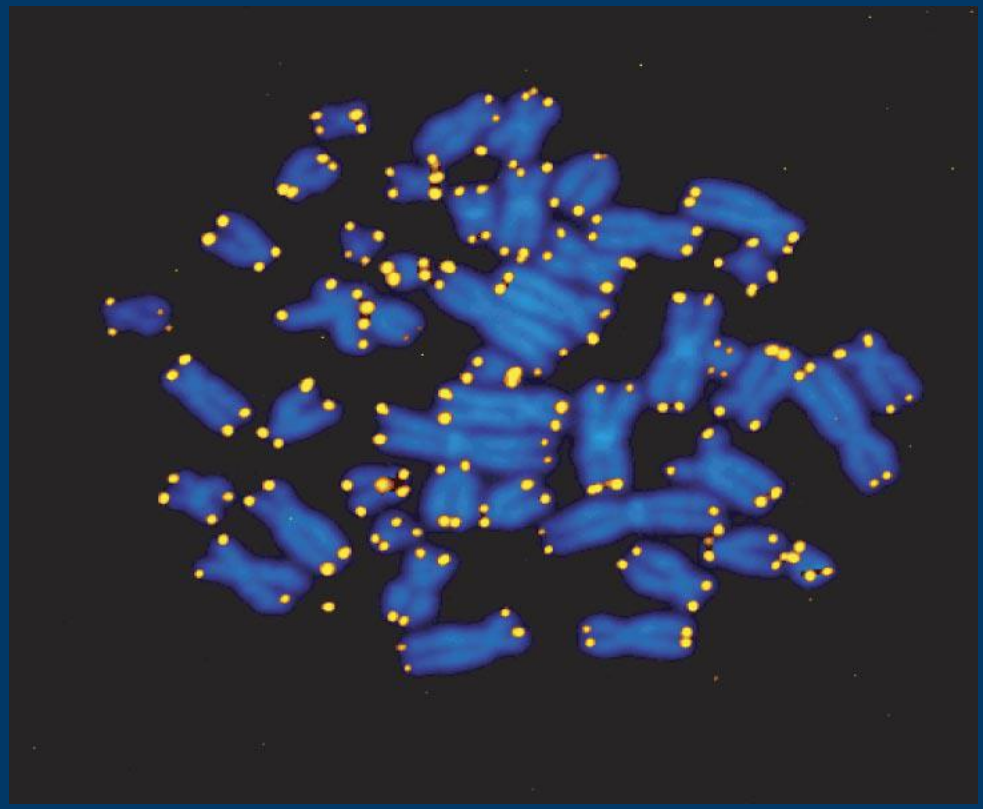
Telomere length: Measurement techniques

- **How to measure**
  - **TRF**: Terminal restriction fragment
  - **Q-PCR**: Quantitative polymerase chain reaction
    - Spectracell
    - TeloYears
  - **Q-FISH**: Quantitative-florescence in situ hybridization
    - Life Length
    - HT Q-FISH Percent Shortest Telomeres
  - **Flow-FISH**: Florescent in situ hybridization and flow cytometry
    - Repeat Diagnostics
    - Lymphocyte and granulocyte TL

CV: >5%

CV: <5%

CV: 2-3%



Aubert G, Hills M, Lansdorp PM. Telomere Length Measurement - caveats and a critical assessment of the available technologies and tools. Mutat Res. 2012 Feb 1;730(1–2):59–67.

Variability of Telomere and Lipid Testing: Assay and Biological

- **Lipids**
  - Assay CV:T-Cholesterol 2.2-4.2%
  - Biological variability

Interval	Total-C	HDL-C	LDL-C	TG
Day	2.5%	4.5%	7.8%	36%
Month	4.8%	7.7%	9.6%	24%
Year	6.1%	8.4%	13.6%	26%

http://www.clinlabnavigator.com/lipid-variability.html

- **Telomere length**
  - Assay CV: 3.3-5%
  - Biological variability

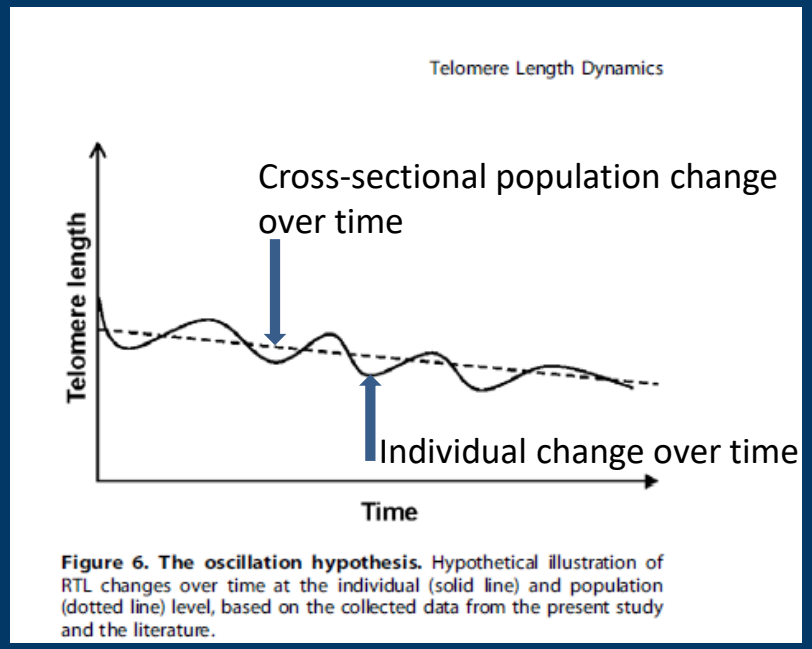
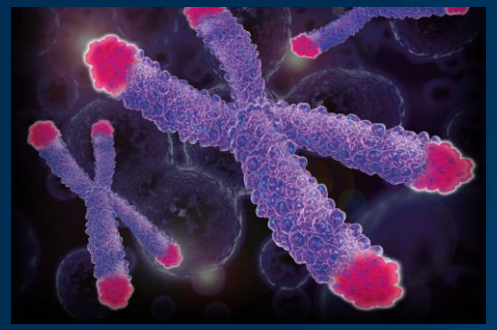


Figure 6. The oscillation hypothesis. Hypothetical illustration of RTL changes over time at the individual (solid line) and population (dotted line) level, based on the collected data from the present study and the literature.

Svenson U PloS ONE 2011



Telomeres 2019

Summary

- Telomere attrition is a major pillar of aging
- Very short telomeres lead to premature death in humans
- Animal models show *rejuvenation* with increase telomerase activity and longer telomeres
- Relatively shorter telomeres are associated with most diseases of aging in humans
- Telomere shortening *even before* replicative senescence alters gene expression
- Clinical trials testing telomere lengthening to prevent recurrent MI and to treat Alzheimer's disease are under way

Recommendations

- Measure telomere length in all your patients
  - Screen for Telomeropathies
  - Risk assessment for chronic diseases
- Reduce stress to maintain telomere length
  - Oxidative, psychological, inflammatory
- Track telomere length q6-12 months
  - A loss greater than 0.05 kb/yr is concerning
  - Assess status of your Biological 401k
- Consider telomerase activator to maintain optimal telomere length
  - Age 25 and older may benefit
- Consider patients with advanced disease for clinical trials of telomerase gene therapy

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THANK YOU!

Slides available on www.physioage.com