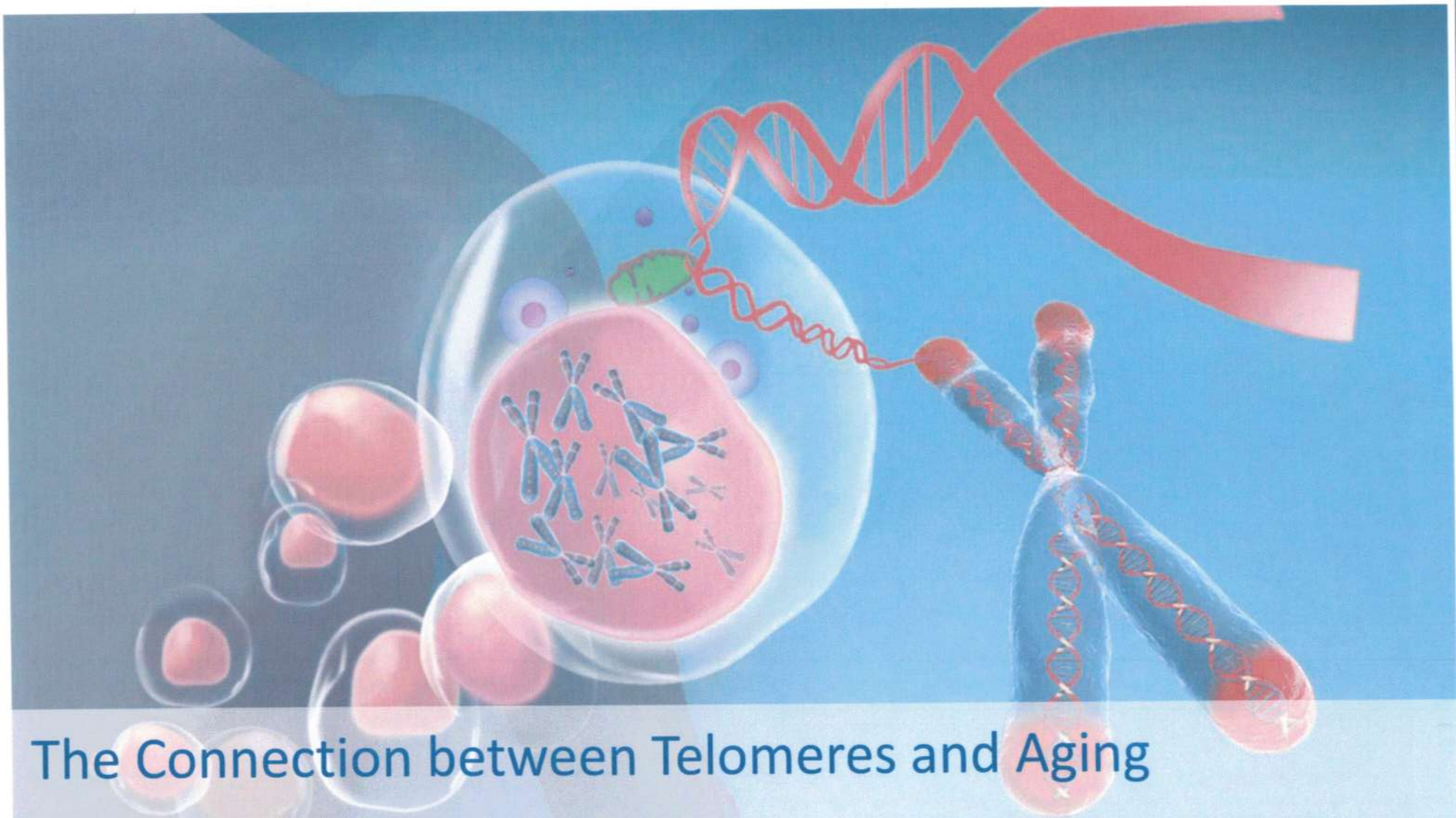


The Connection between Telomeres and Aging

September 2015

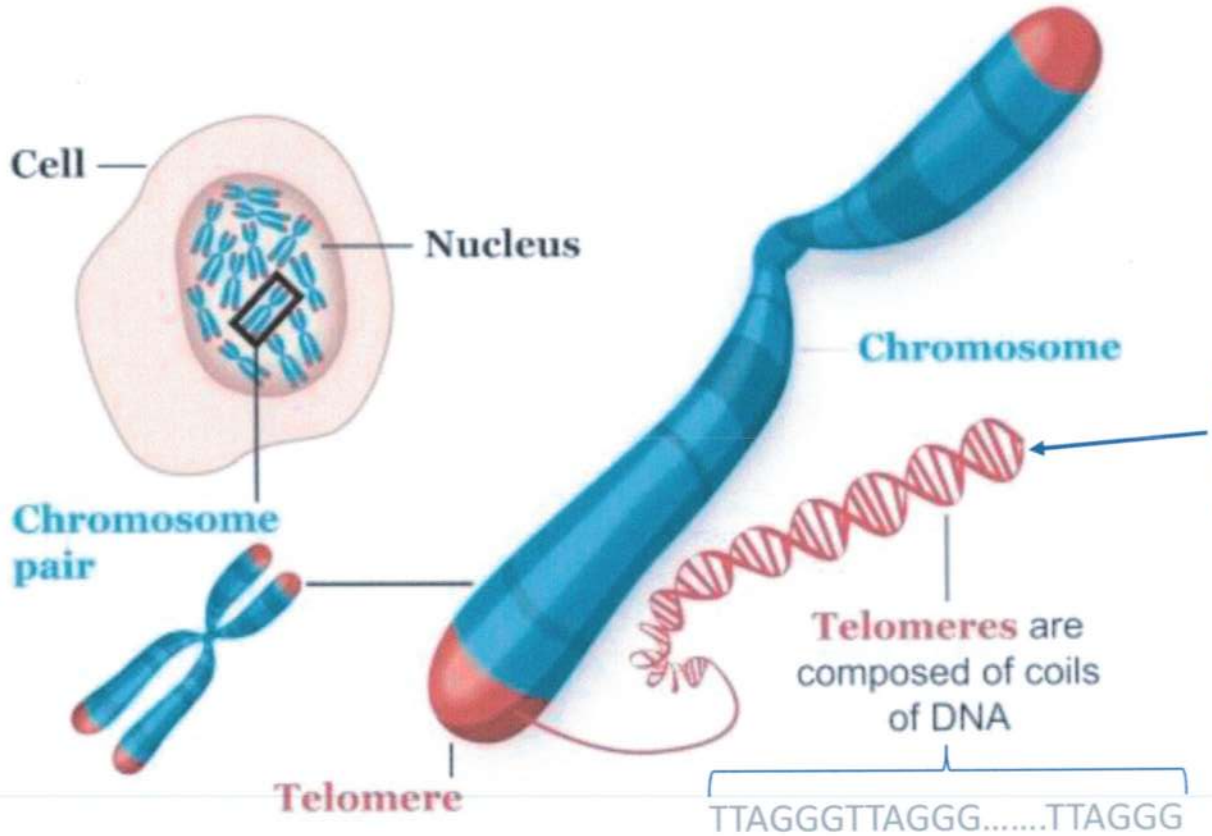
LIFE LENGTH

"If I'd known I was going to live this long, I'd have taken better care of myself" –

Eubie Blake, 96 years old

What are telomeres and why are they so important in preventive medicine?

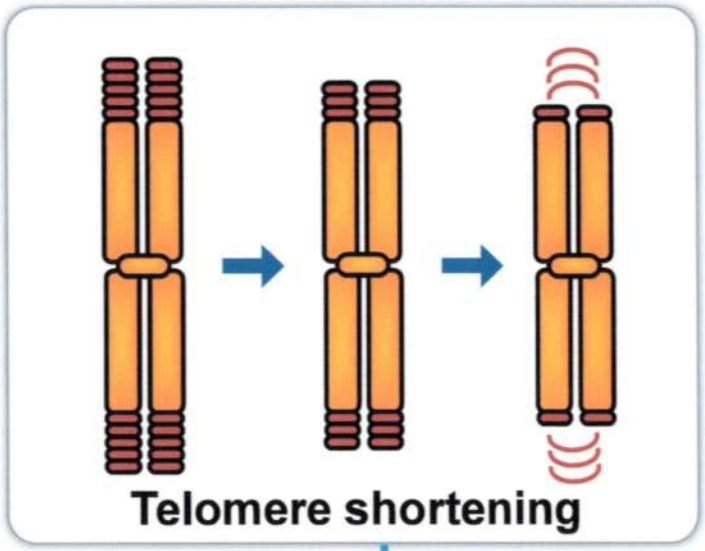
Telomeres are the protective caps at the end of chromosomes which play a very significant role in the aging process

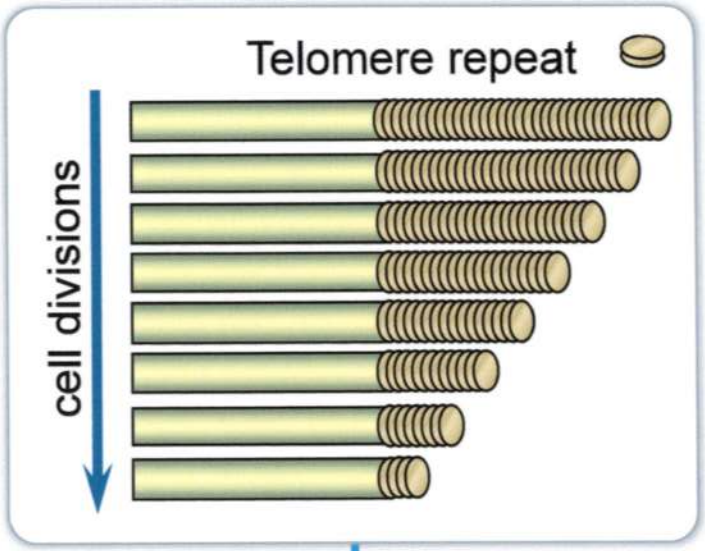


A labeled probe containing the complementary sequence can be used to detect the telomere

What is a telomere's function?

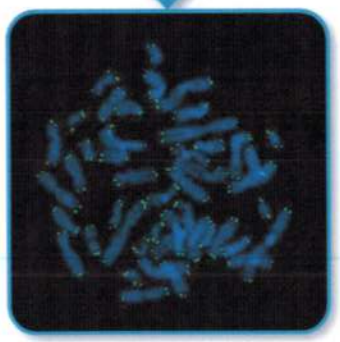
All chromosomes are capped by telomeres
TELO (end) **MERE** (segment)

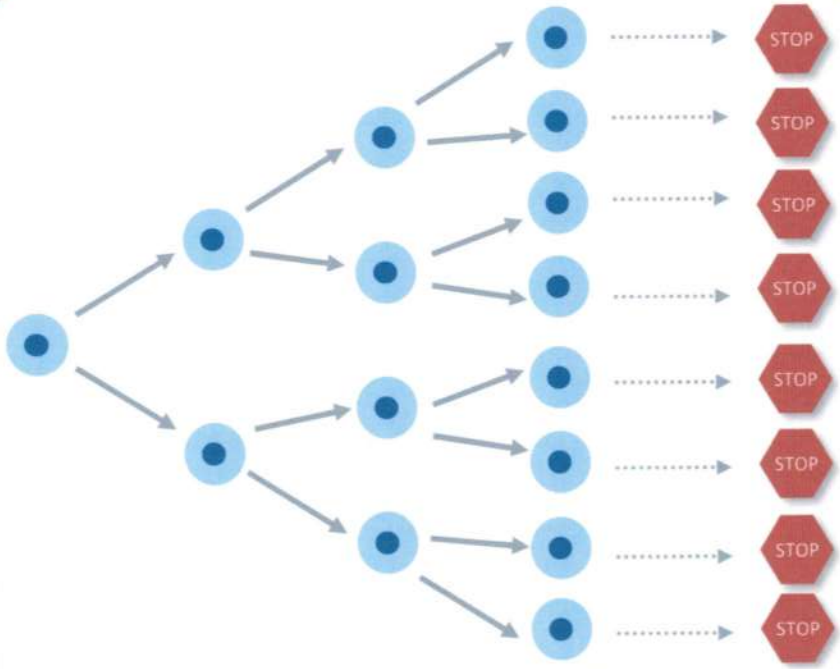




Senescence

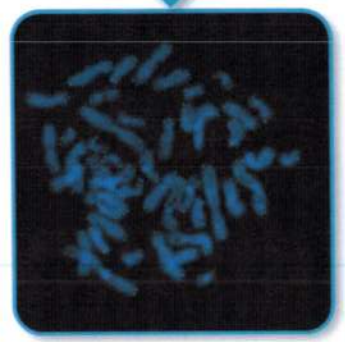
Normal cells have a limited replicative capacity





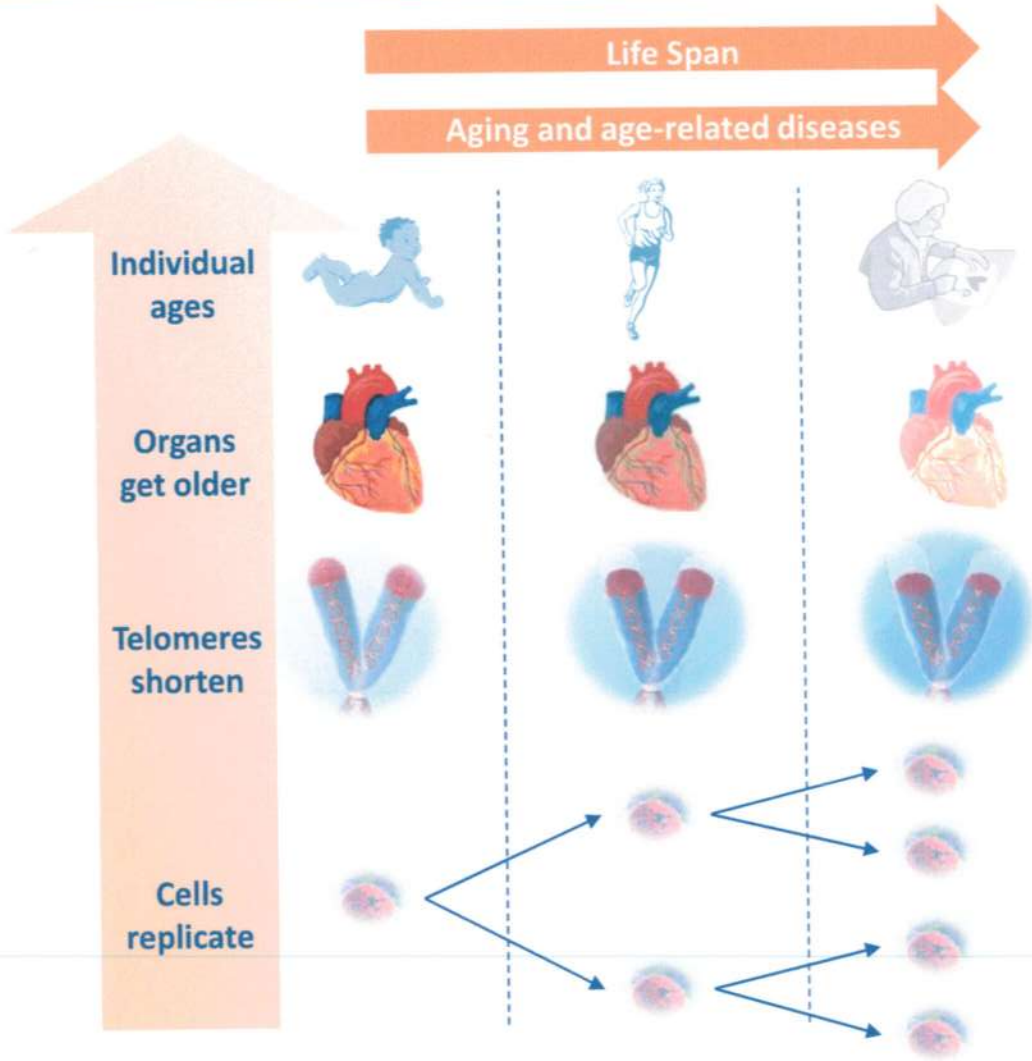
- Cell grows during 50-80 doublings, depending on specific cell type.
- This phenomenon is known as the **Hayflick limit.**

Hayflick, 1950s



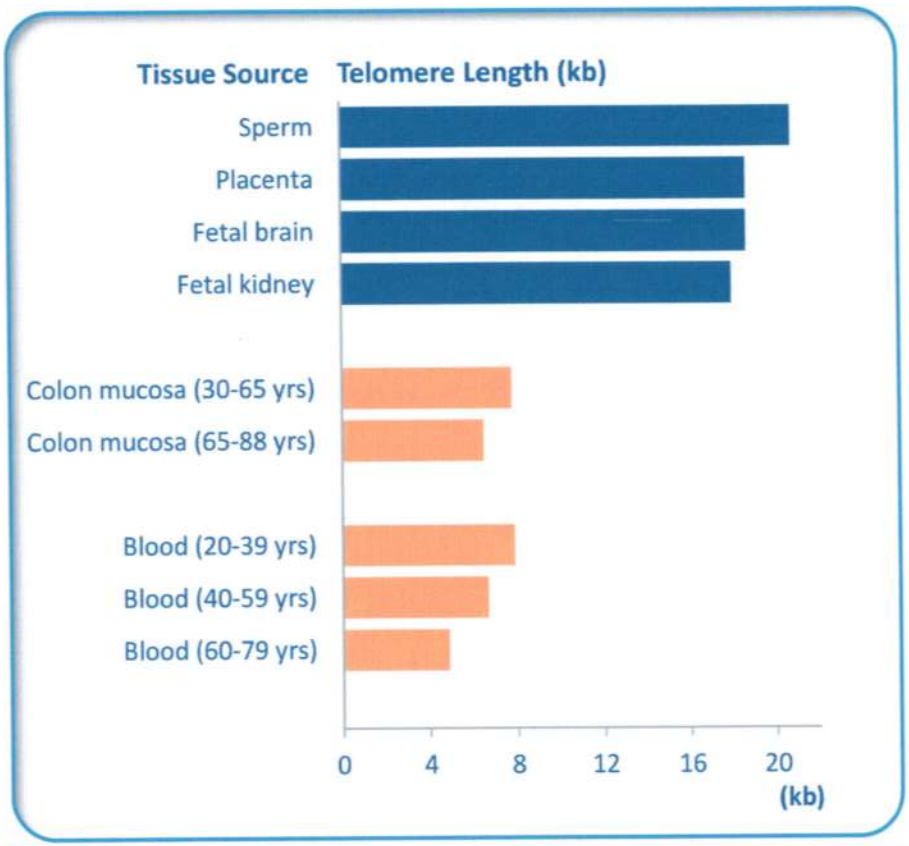
Telomere length is one of the most critical biomarkers for human aging and in the early diagnosis of age-related diseases

- In any living organism, aging is the result of the decrease in the number and/or function of cells
- Every time cells replicate, telomeres shorten until they reach a point where the cells can no longer divide properly
- Cells with such short telomeres usually become senescent or enter apoptosis, and eventually die
- Therefore, telomere length is a crucial biomarker providing insight into understanding organismal aging

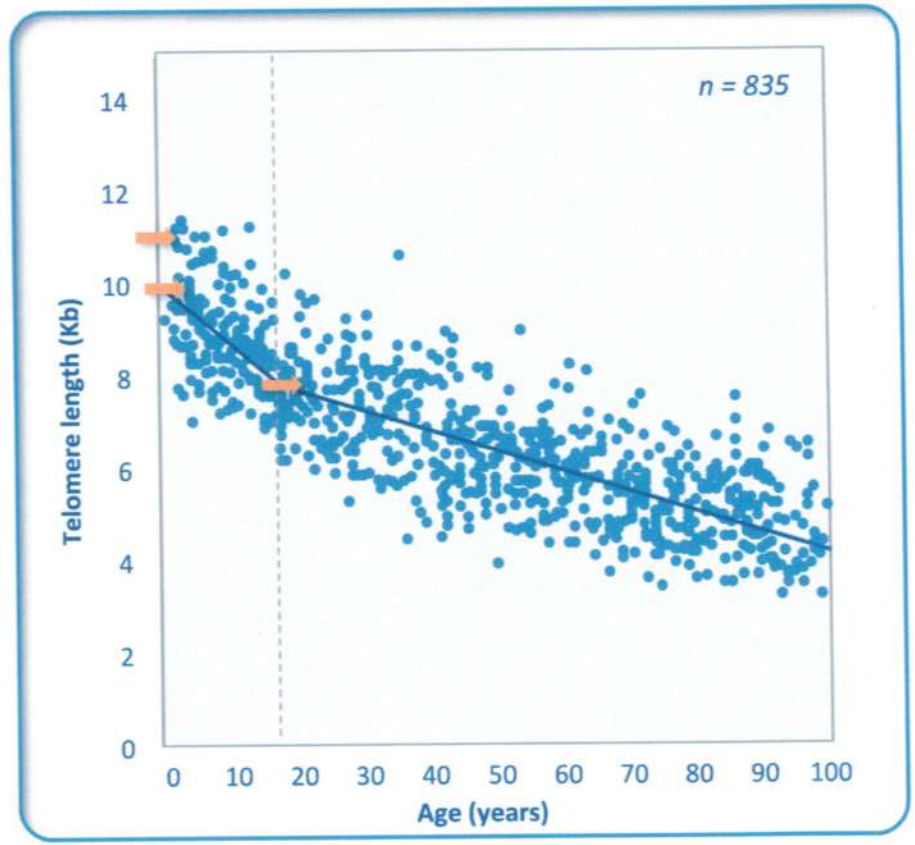


LIFE LENGTH

Telomere shortening occurs at the organismal level but is highly heterogeneous in rate



Source: Hastie et al., Nature, 1990

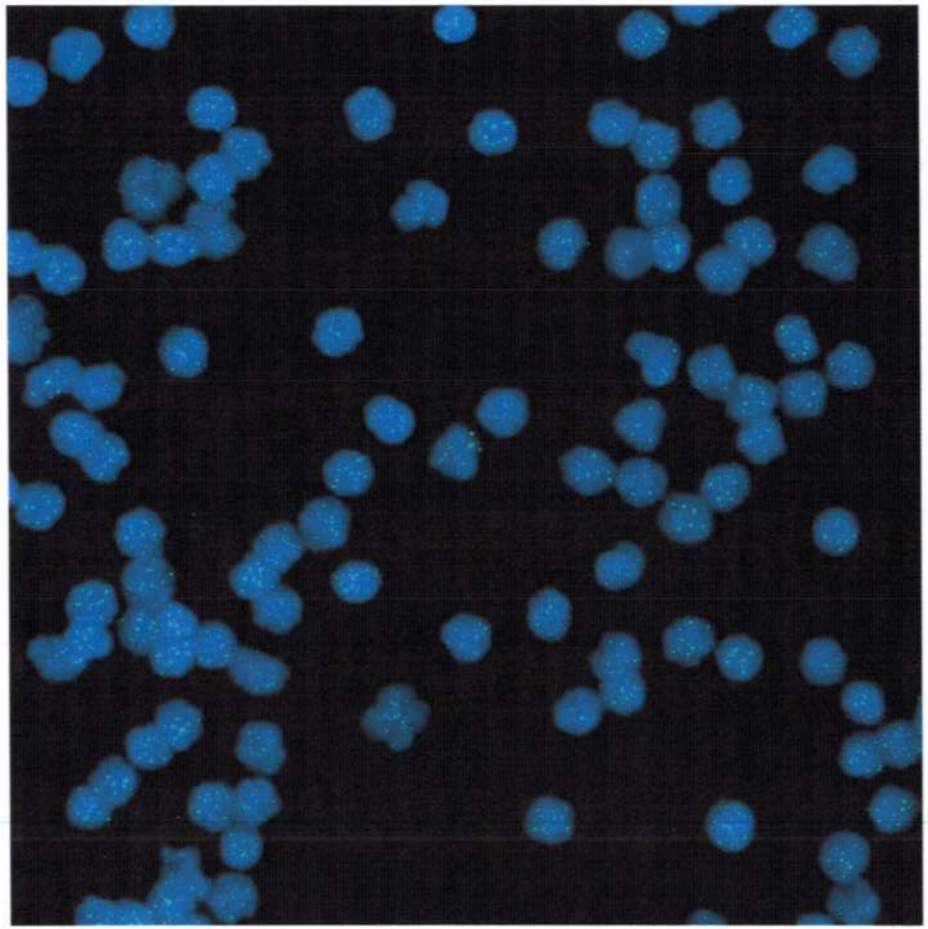


Source: Aubert et al., Plos Genetics, 2012

Shorter telomeres correlate with increased age

LIFE LENGTH

Why should you care about telomeres?



Adverse consequences of short telomeres:

- Loss of tissue renewal capacity; failure of stem cells to divide in sufficient numbers
- Senescent-associated secretory phenotype (SASP):
  - ✓ Inflammation
  - ✓ Decrease immune responses

It is well established that telomeres contribute to the development of age-related diseases:

- Cardiovascular diseases
- Metabolic diseases
- Cancer

Influence of Telomeres **on Cardiovascular Health**

Reduced telomere lengths are found in patients with cardiovascular risk factors such as:

- Atherosclerosis
- Hypertension
- Obesity
- Diabetes (especially Type 2)
- Smoking
- Physical inactivity
- Stress
- Chronic infections
- Shorter telomeres have been associated with poor survival

A positive effect on telomere length is found with increased physical activity, statin treatment, and higher blood levels of omega-3 fatty acids

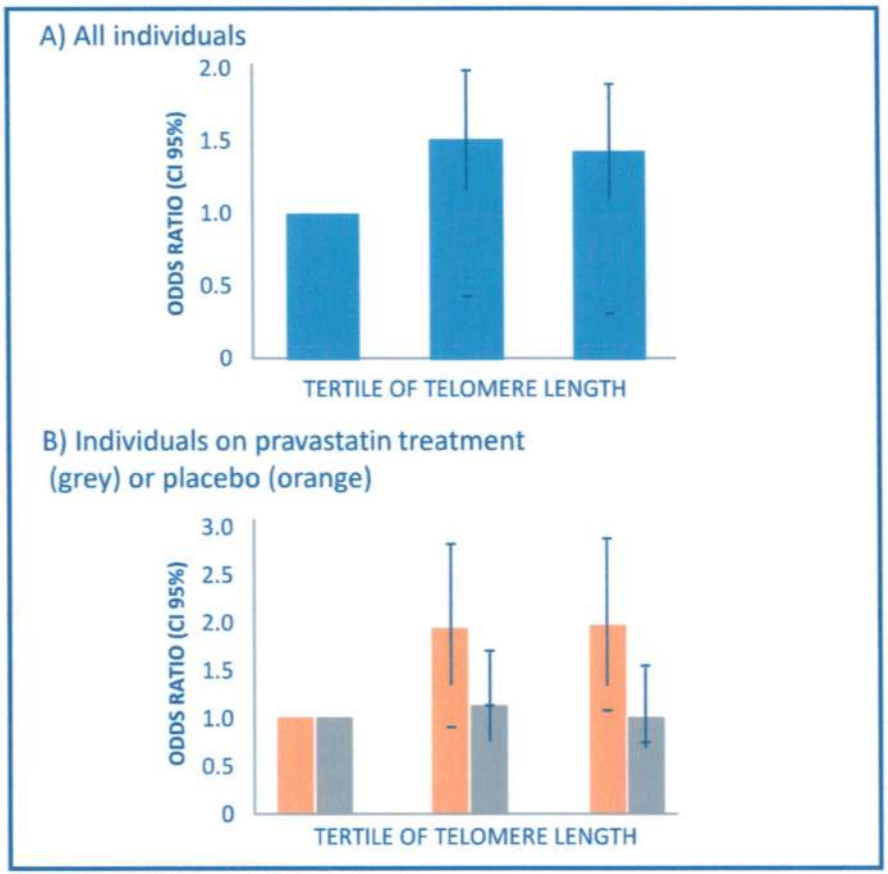
Cardiovascular disease risk stratification through telomere length analysis

- **Telomere length** has now been demonstrated to be an **independent risk factor** for **CVD**
- **Telomere testing** is being used to **complement traditional cardiovascular** tests in order to provide a more comprehensive analysis and even identify the risks of developing cardiovascular problems at an **earlier** stage
- **Telomere measurement** can identify **high risk** individuals with short telomeres

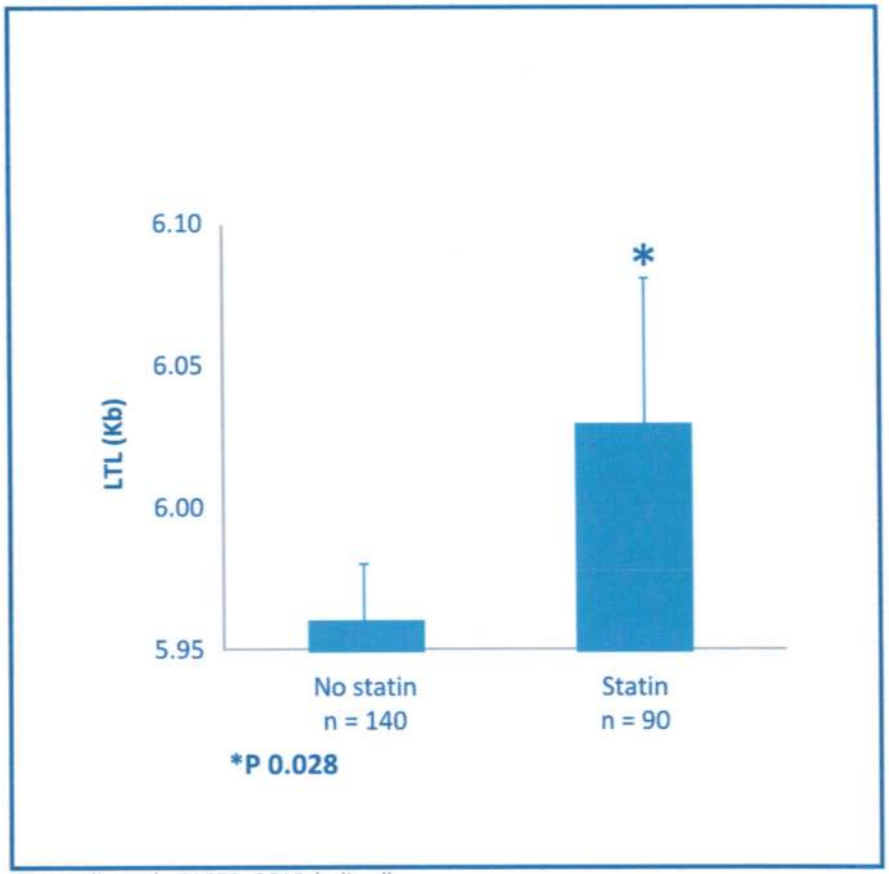
The **British Medical Journal** has published a study of more than 43,000 participants which concluded that telomere length is an **independent risk factor** for cardiovascular disease

LIFE LENGTH

Coronary Heart Disease, Statins and Telomere Length



Brouilette et al., Lancet, 2007 (edited)



Boccardi et al., FASEB, 2013 (edited)

Statins may extend lives by not only lowering cholesterol levels but also protecting against telomere shortening, **thus reducing the risk** of cardiovascular disease and other age-associated diseases

Cardiometabolic disease and telomere length

- **Cardiovascular disease** and **Type 2 Diabetes** are two disorders clearly related to **age** and reduced life and healthspan

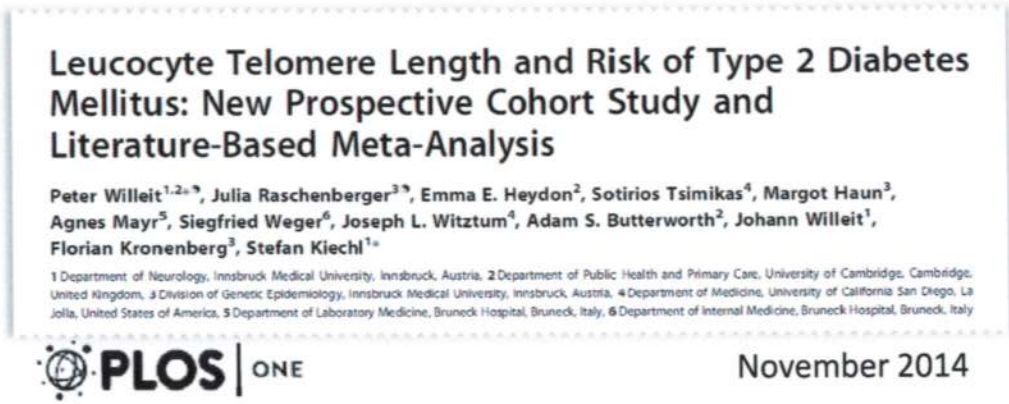
Circ Cardiovasc Genet. 2015 Feb;8(1):82-90. doi: 10.1161/CIRCGENETICS.113.000485. Epub 2014 Nov 18.

Association between shortened leukocyte telomere length and cardiometabolic outcomes: systematic review and meta-analysis.

D'Mello MJ[1], Ross SA[1], Briel M[1], Anand SS[1], Gerstein H[1], Paré G[2].

- Short telomere length is associated with arterial aging in patients with Type 2 Diabetes
- Telomere analysis may serve to **detect individuals** at a **high risk** for developing this disease

Type 2 Diabetes and telomeres



Leucocyte Telomere Length and Risk of Type 2 Diabetes Mellitus: New Prospective Cohort Study and Literature-Based Meta-Analysis

Peter Willeit[1,2*], Julia Raschenberger[3], Emma E. Heydon[2], Sotirios Tsimikas[4], Margot Haun[3], Agnes Mayr[5], Siegfried Weger[6], Joseph L. Witztum[4], Adam S. Butterworth[2], Johann Willeit[1], Florian Kronenberg[3], Stefan Kiechl[1*]

1 Department of Neurology, Innsbruck Medical University, Innsbruck, Austria, 2 Department of Public Health and Primary Care, University of Cambridge, Cambridge, United Kingdom, 3 Division of Genetic Epidemiology, Innsbruck Medical University, Innsbruck, Austria, 4 Department of Medicine, University of California San Diego, La Jolla, United States of America, 5 Department of Laboratory Medicine, Bruneck Hospital, Bruneck, Italy, 6 Department of Internal Medicine, Bruneck Hospital, Bruneck, Italy

PLOS | ONE

November 2014

- **Telomere analysis** can be used to detect individuals at risk of developing metabolic diseases, particularly at a younger age, such as **Type 2 Diabetes**
- Recent studies demonstrate that short telomere length is associated with future development of **Type 2 Diabetes** independently of the known risk factors
- These studies show that individuals in the lowest quartile of **leucocyte telomere length** had twice the risk of developing diabetes than those with longer telomeres

Influence of telomeres in **Cancer**

"Global burden of cancer will rise from" an estimated 14 million new cases per year in 2012 to 22 million within the next 20 years."

World Health Organization

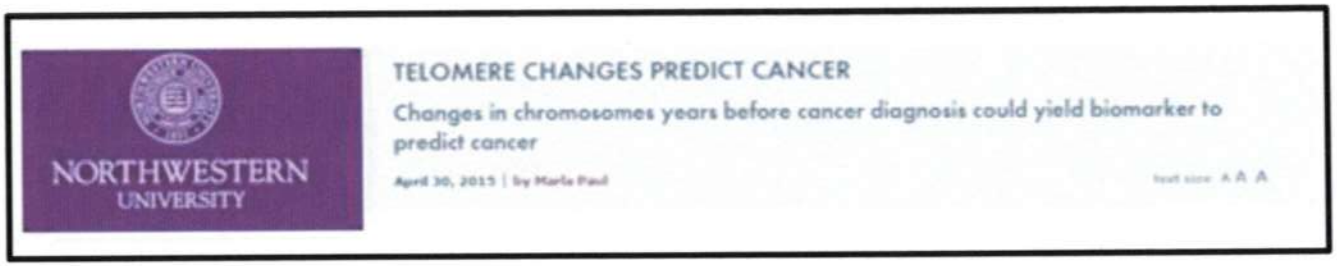
Short telomeres have been shown to be a risk factor for certain types of cancer:

- Breast
- Ovarian
- Uterine
- Prostate
- Skin cancers

This is especially relevant in individuals with family history

Influence of telomeres in **Cancer**

- **Telomere analysis** will help detect high risk individuals with short telomeres - more frequent check-ups at an earlier age
- Patients with **BRCA1/2** and short telomeres develop breast cancer at a younger age than those with longer telomeres
- Individuals with short telomeres have been demonstrated to have higher probability of developing **secondary cancers**
- Several studies are being conducted to evaluate the potential clinical use of telomeres in non-small cell **lung cancer**


NORTHWESTERN UNIVERSITY

TELOMERE CHANGES PREDICT CANCER

Changes in chromosomes years before cancer diagnosis could yield biomarker to predict cancer

April 30, 2015 | by Marla Paul

ORIGINAL ARTICLE

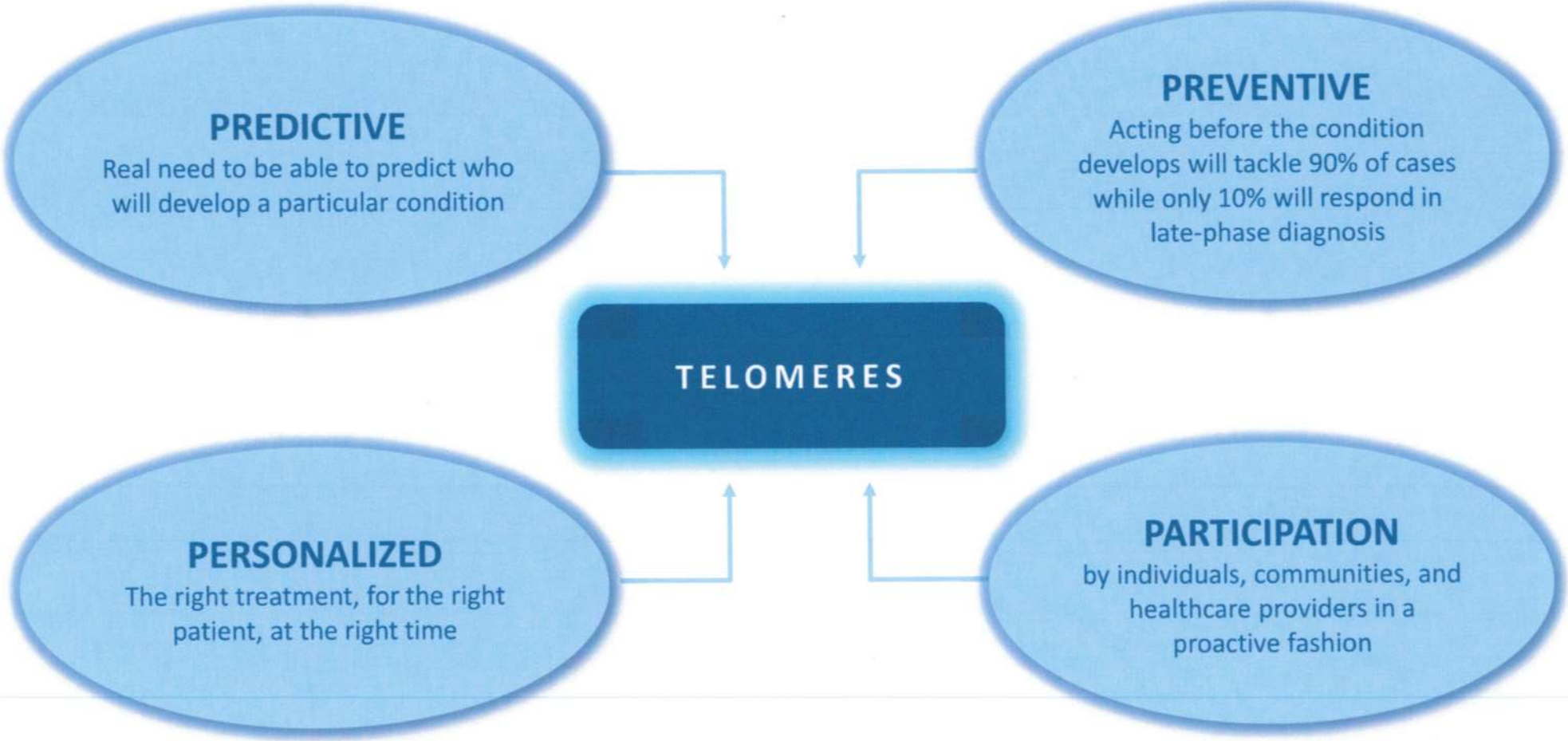
Genetic determinants of telomere length and risk of common cancers: a Mendelian randomization study

Hematologic Cancer and telomeres

- **Chronic lymphocytic leukemia:** Telomere length is associated with disease progression and response to treatment
- **Myelodysplastic syndromes (MDS)**
  - 1 out of 3 MDS progresses into Acute Myeloid Leukemia –age-related telomere shortening has a role in chromosome instability in AML development
  - New compounds targeting telomerase in the clinic: Myelofibrosis, MDS and AML
- **Hematopoietic Stem Cell Transplantation**
  - Studies are being conducted to elucidate the role of telomeres in Hematopoietic Stem Cell Transplantation
  - Longer donor **leukocyte telomere length** may have a role in long-term post-transplant survival

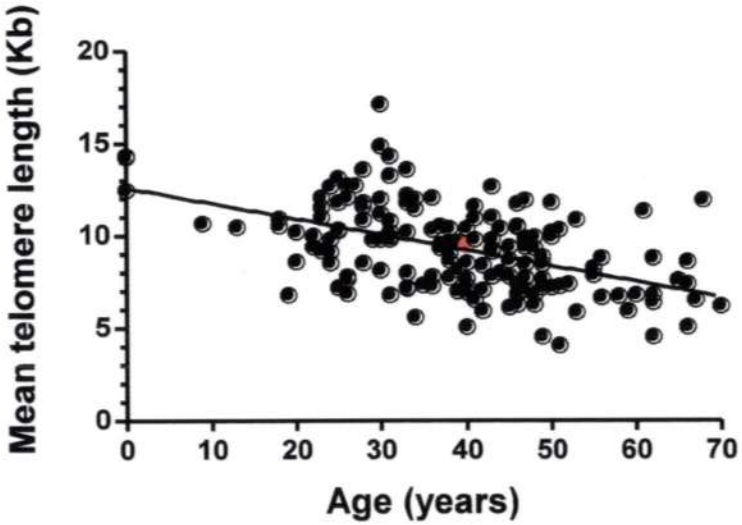
Life Length's TAT may serve for **prognosis** and to **measure treatment response**

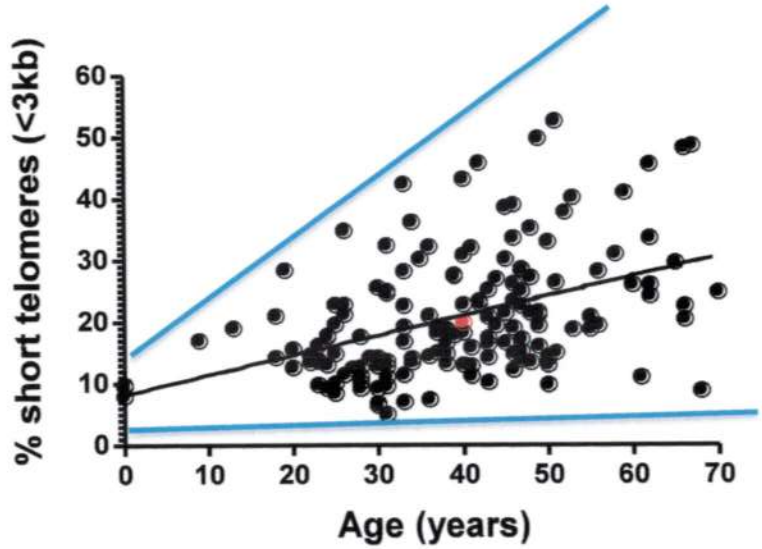
Why use **telomere length** determinations in your medical practice?



LIFE LENGTH

The % of short telomeres, not average telomere length determines the onset of disease

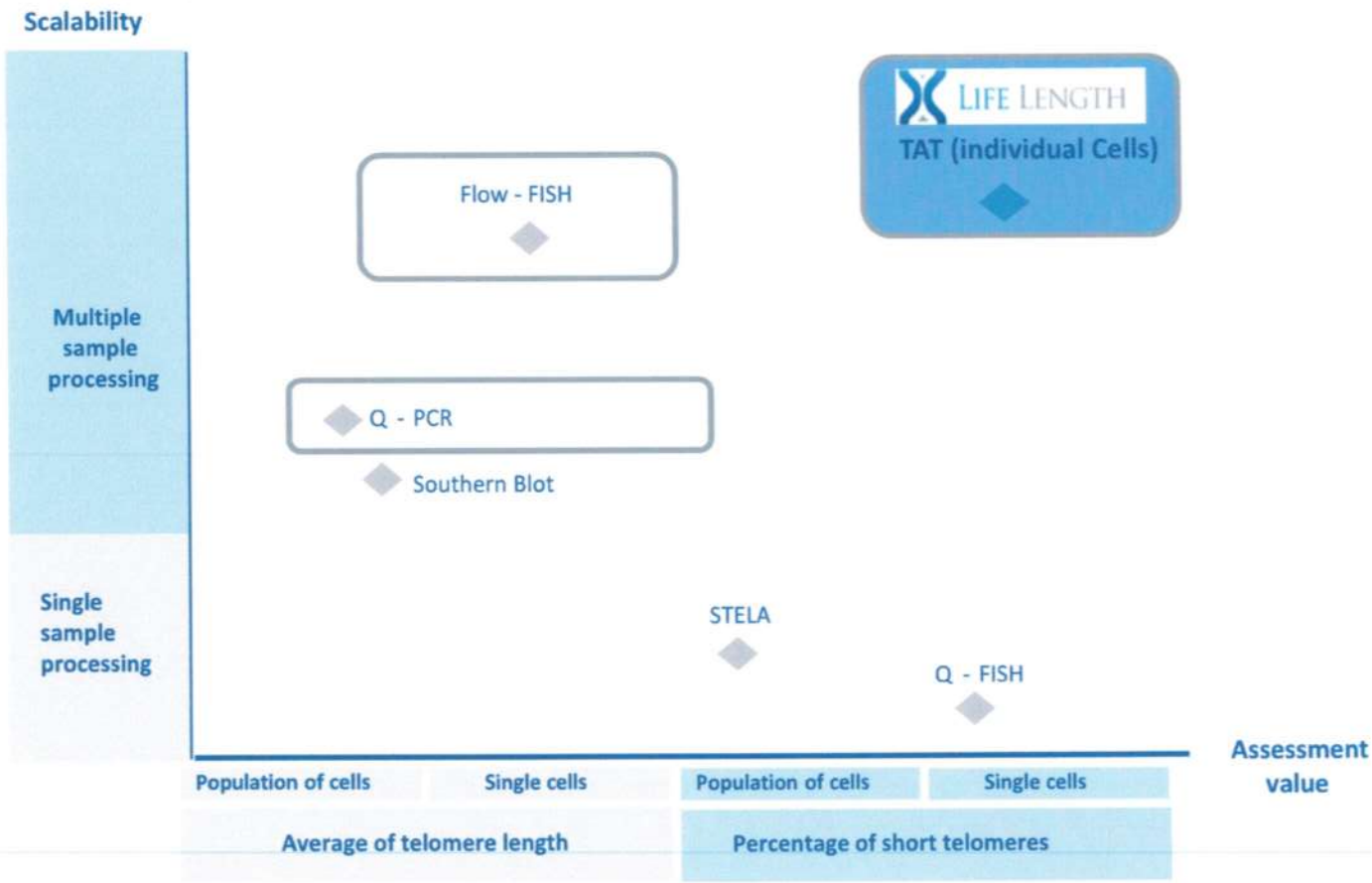




- Percent of short telomeres detect more differences between individuals than average length
- Percent of short telomeres show higher scattering as we age
- Percent of short telomeres reflect genetic, environmental and lifestyle habits

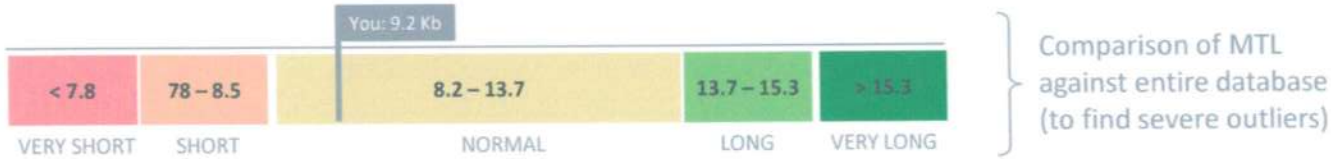
LIFE LENGTH

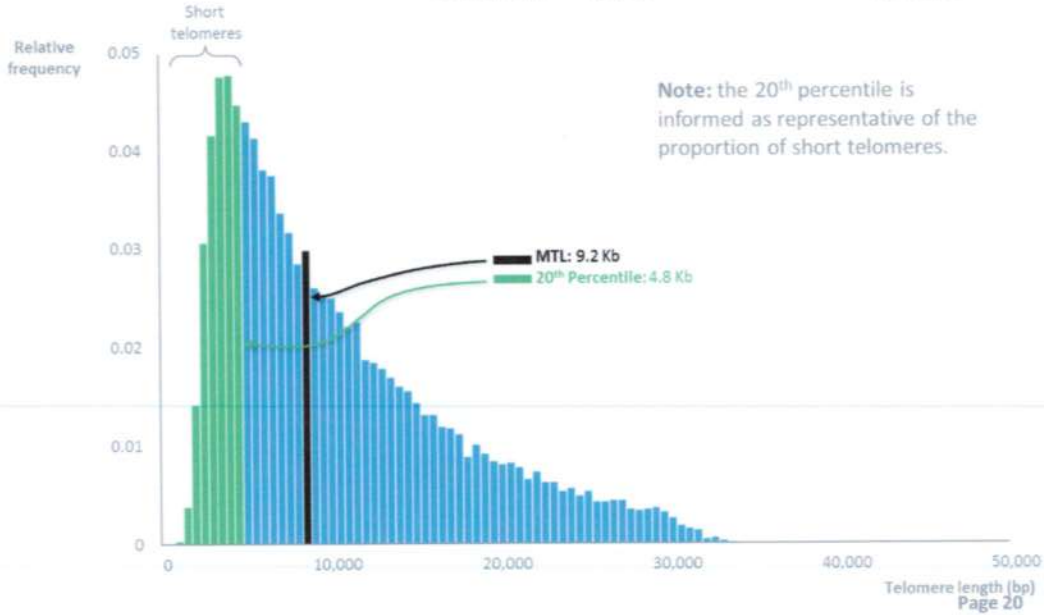
Methods for measuring telomere length



Life Length's Telomere Analysis Technology® (TAT®)

- Life Length is the only company in the world able to measure the **percentage of short telomeres** in individual cells, which is the **relevant indicator** of cellular aging, rather than mean telomere length
- The TAT test is a blood test that measures the length of **thousands of individual telomeres** to reveal a person's **cellular or biological age**, the age a person shares with most people of similar **physiology**





Note: the 20th percentile is informed as representative of the proportion of short telomeres.

TELOMERE ANALYSIS TECHNOLOGY

LIFE LENGTH

Telomere length integrates genetic and environmental factors

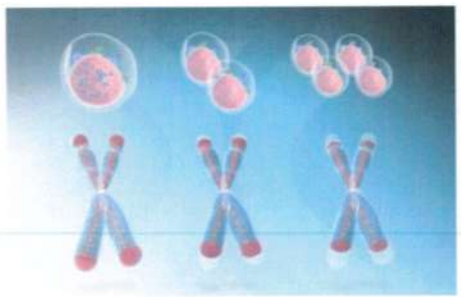
Biomarkers for prevention and diagnostics

GENETICS
+
ENVIRONMENTAL
+
LIFE STYLE

TELOMERES

CONSEQUENCES

Infancy → Youth → Adulthood



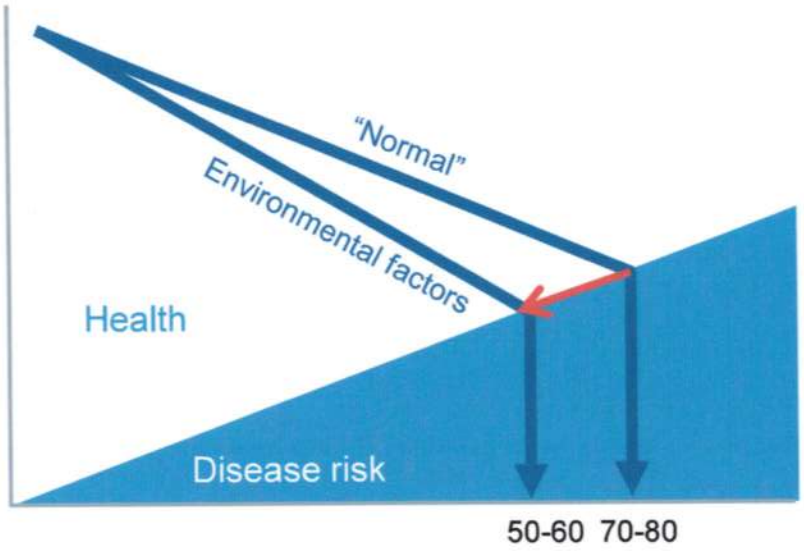
Aging

CANCER
CARDIOVASCULAR
DIABETES
KIDNEY DISEASE
NEURODEGENERATION

EARLY Therapeutic Interventions:
Outcome – Longer life / health span
Lower costs – more productive individuals and society

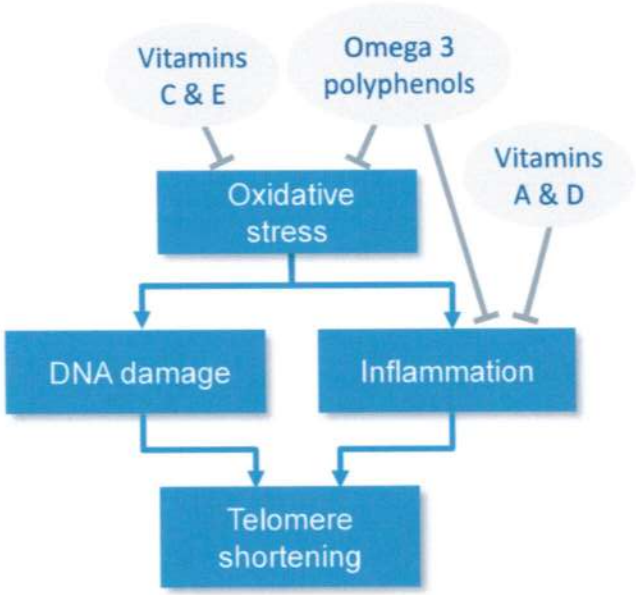
LATE Therapeutic Interventions:
Shorter life / health span
Much greater costs – less productive individuals and society

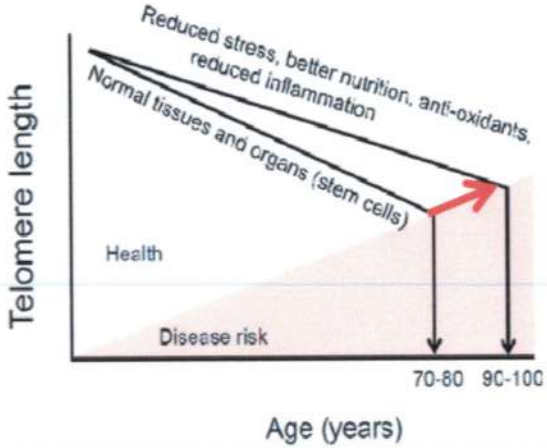
Lifestyle and environmental factors that accelerate telomere shortening



- Chronic stress
- Poor diet and nutritional habits
- Lack of certain key vitamins
- Chronic inflammatory diseases
- Metabolic disorders
- Sedentary lifestyle
- Obesity, high BMI and body fat
- Smoking
- Over consumption of alcohol
- Lack of sleep / insomnia

Reducing inflammation and **oxidative stress** slows telomere shortening





- Incorporate dietary supplements such as:
  - Vitamin C and E
  - Omega 3 polyphenols
  - Vitamins A and D
- A healthy diet improves healthspan

Mediterranean diet and telomere length

Genetic factors may contribute to the link between Mediterranean diet and longer telomeres

Peter M Nilsson *professor*

Lund University, Department of Clinical Sciences, Skåne University Hospital, S-205 02 Malmö, Sweden

thebmj

December 2014

Telomere measurement can be used to monitor the benefits of a healthy lifestyle

LIFE LENGTH

Conclusion: An Invaluable Tool for Your Medical Progress

Measuring telomeres will allow you:

1. To risk stratify patients and identify individuals with accelerated biological aging
2. To enable early intervention-lifestyle modifications to reduce stress, inflammation, oxidative damage and other inducers of accelerated telomere loss
3. To provide therapeutic interventions to slow down or reverse telomere loss (stem cells, bone marrow transplantations to select optimal donors, tissue engineering, supplements)
4. To complement other testing (traditional and genetic) for the predictive diagnosis of disease and to take action accordingly
5. To measure longitudinally patient's cellular/biological aging over time to monitor the effectiveness of wellness/anti-aging programs

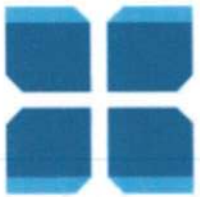
Progress in science depends on **new techniques, new discoveries** and **new ideas,** probably in that order –

Sydney Brenner

LIFE LENGTH

What is required to take the **TAT**?

- Our test is a blood test that measures the length of **thousands of individual telomeres** to reveal a person's **cellular or biological age**, the age a person shares with most people of similar **physiology**
- It is **simple** for doctors and patients because fasting and preparation for blood collection is not required
- **12 - 18 ml of blood is needed** (depending on standard tube sized used)
- It is essential to complete an online anonymous health questionnaire: (www.lifelength-questionnaire.com)
- A detailed Results Report is provided, available in 13 languages
- The physician receives the results of patient samples in approximately two to four weeks



TELOMERE
ANALYSIS
TECHNOLOGY

LIFE LENGTH