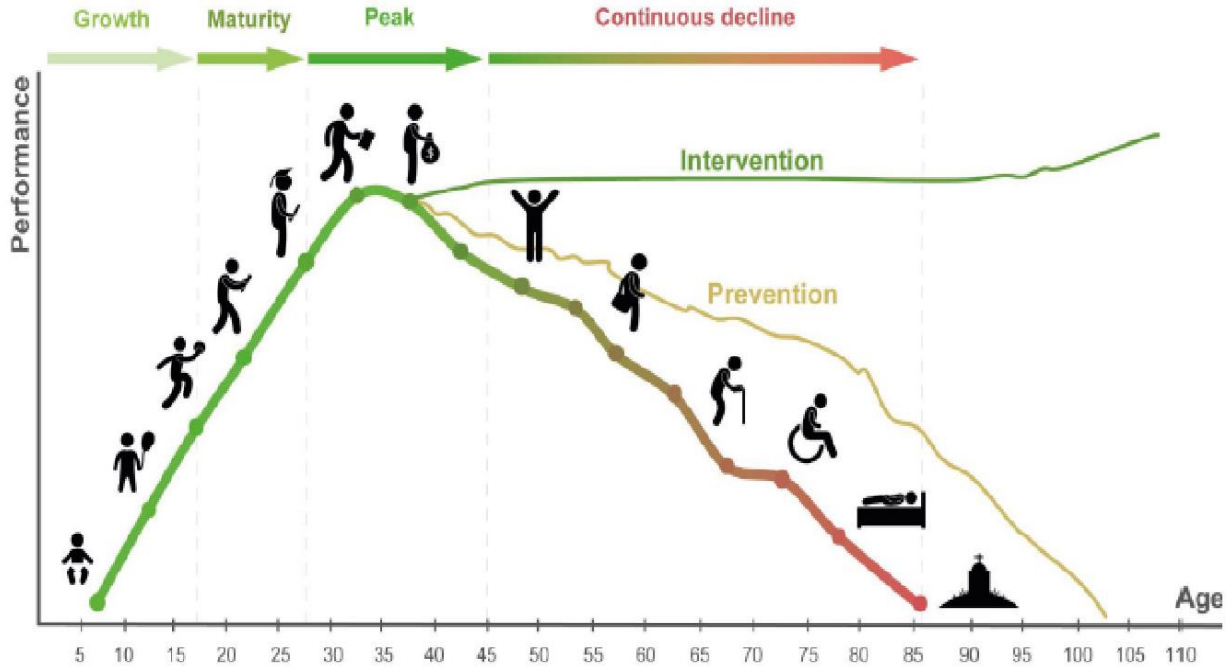
Biomarcatori di longevità

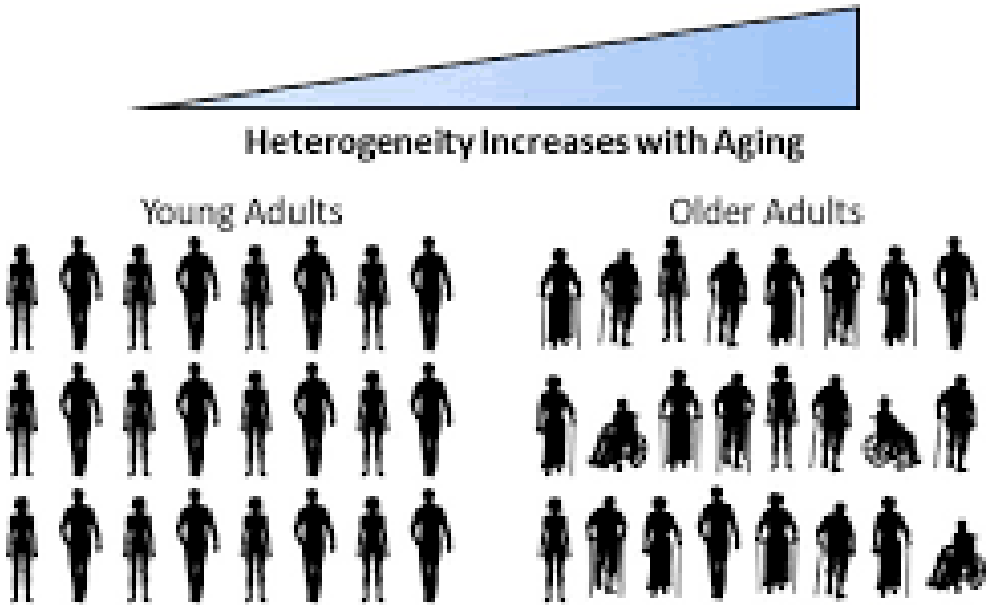
Dott.ssa Fabrizia Lattanzio

Direttore Scientifico IRCCS INRCA e Presidente Rete Aging

Roma, 30 novembre 2022

HETEROGENEITY OF AGING

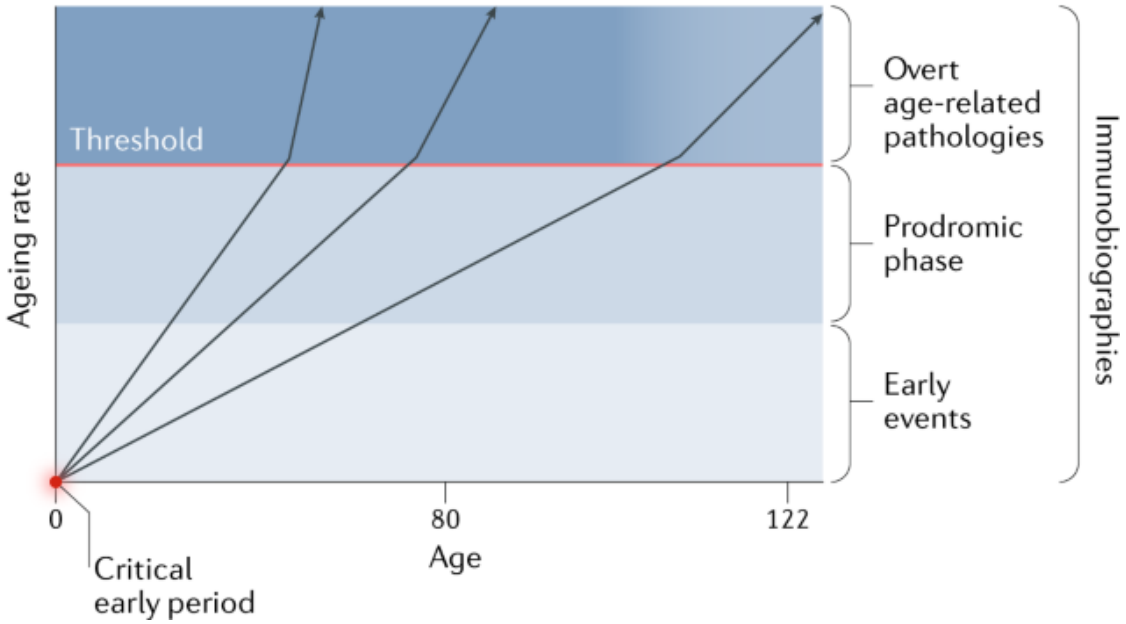




www.aging-us.com AGING 2019, Vol. 11, No. 22

Inflammaging

Schematization of <u>different age-trajectories</u>, corresponding to accelerated, normal, or successful aging, and reaching the threshold for ARDs at different age.



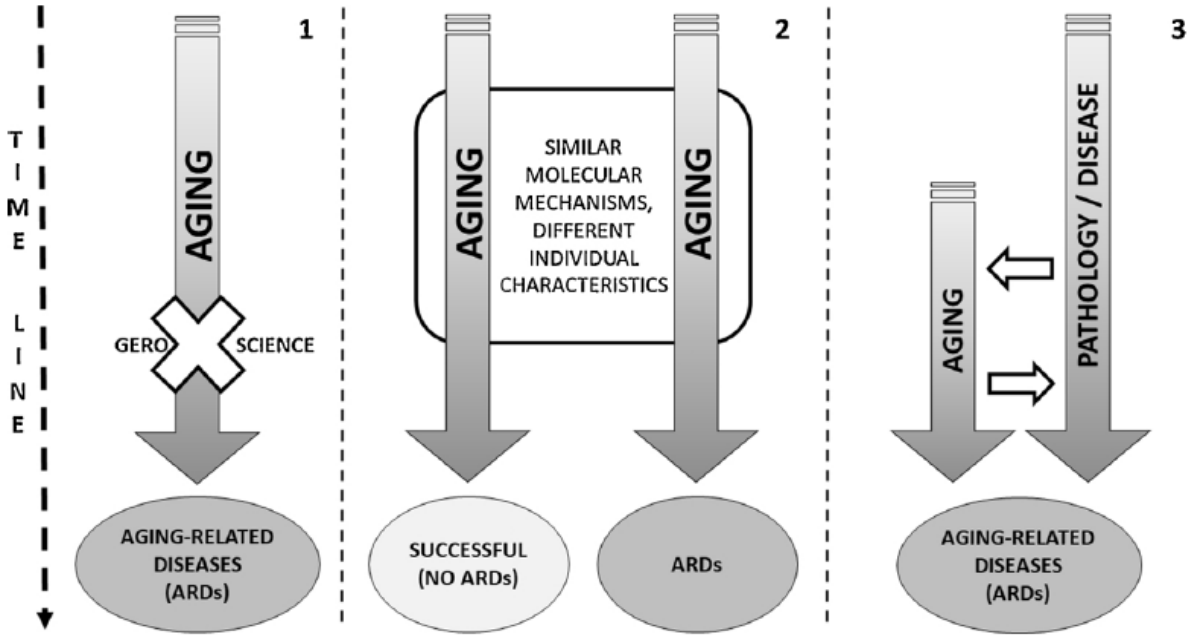
Seminars in Immunology 40 (2018) 17–35
Contents lists available at ScienceDirect
Seminars in Immunology
journal homepage: www.elsevier.com/locate/ysmim

Review

The integration of inflammaging in age-related diseases

Tamas Fulop[a,*], Jacek M. Witkowski[b], Fabiola Olivieri[c,d,**], Anis Larbi[e,f]

Conceptual schematization of the three different approaches to disentangle the relationship between aging and age-related diseases development.

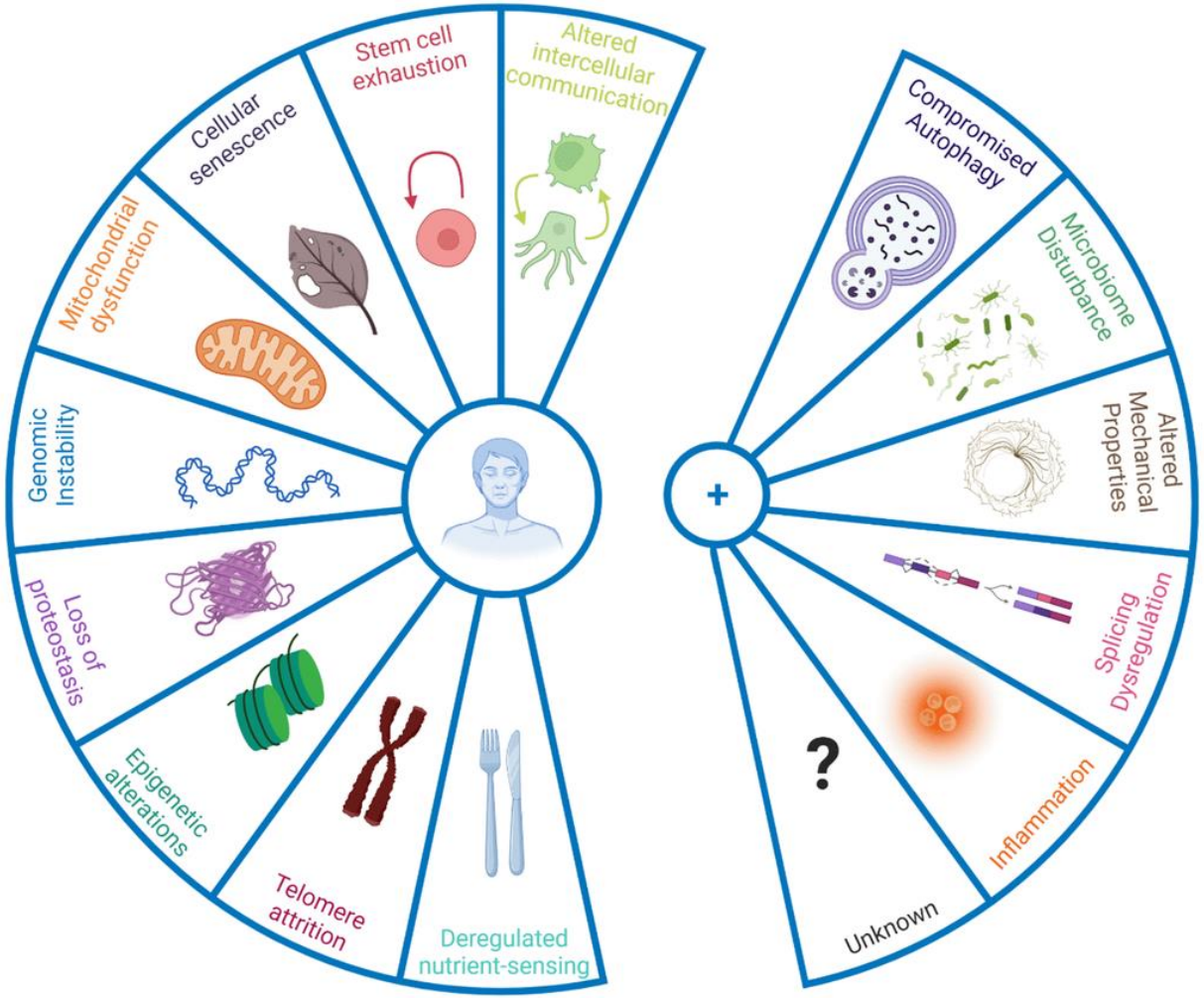


Geroscience

Aging and age-related diseases share common mechanisms

Aging worsen the already existing damages, but not cousing it

The original hallmarks of ageing plus the five new proposed



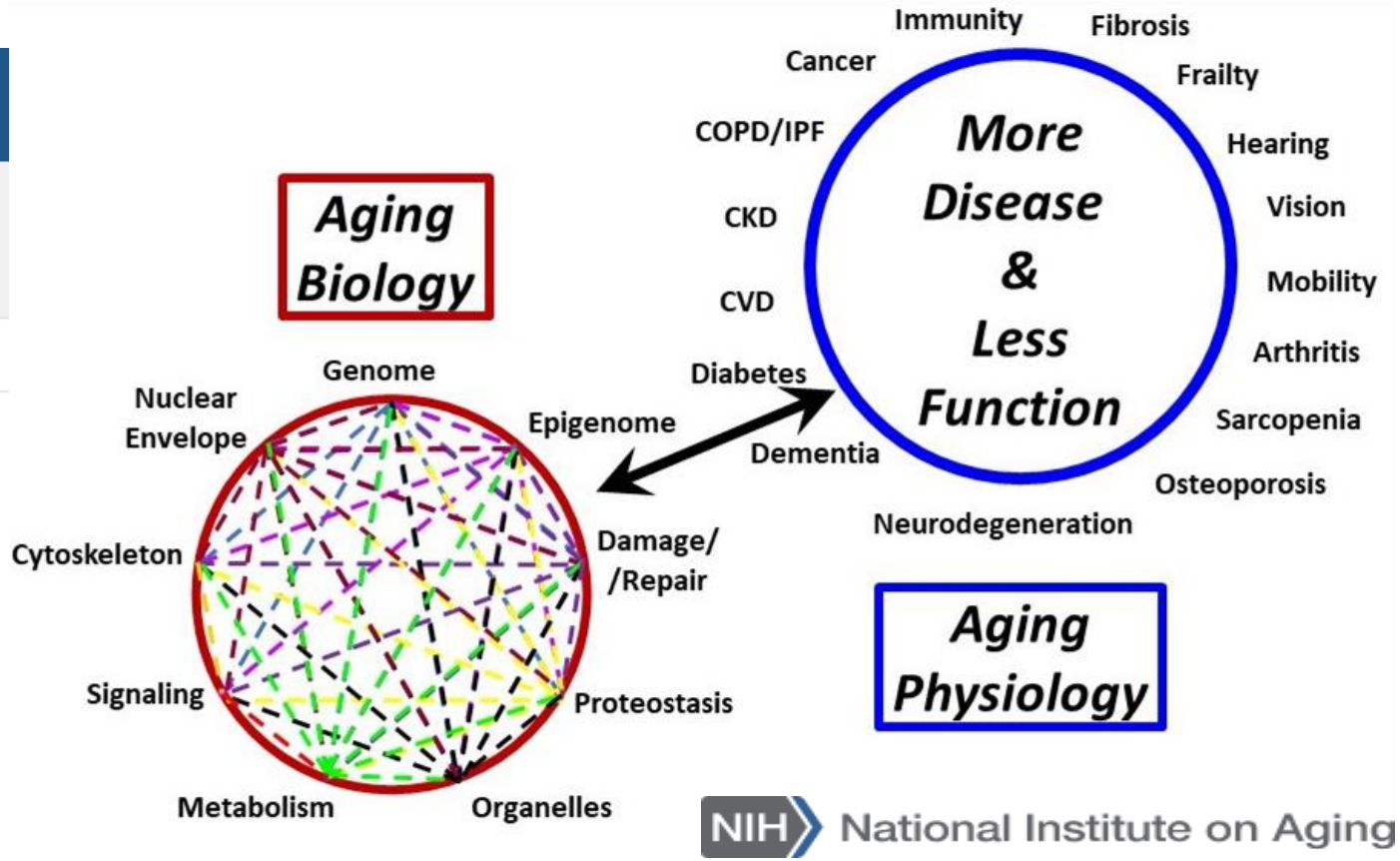
www.aging-us.com AGING 2022, Vol. 14, No. 16

Review

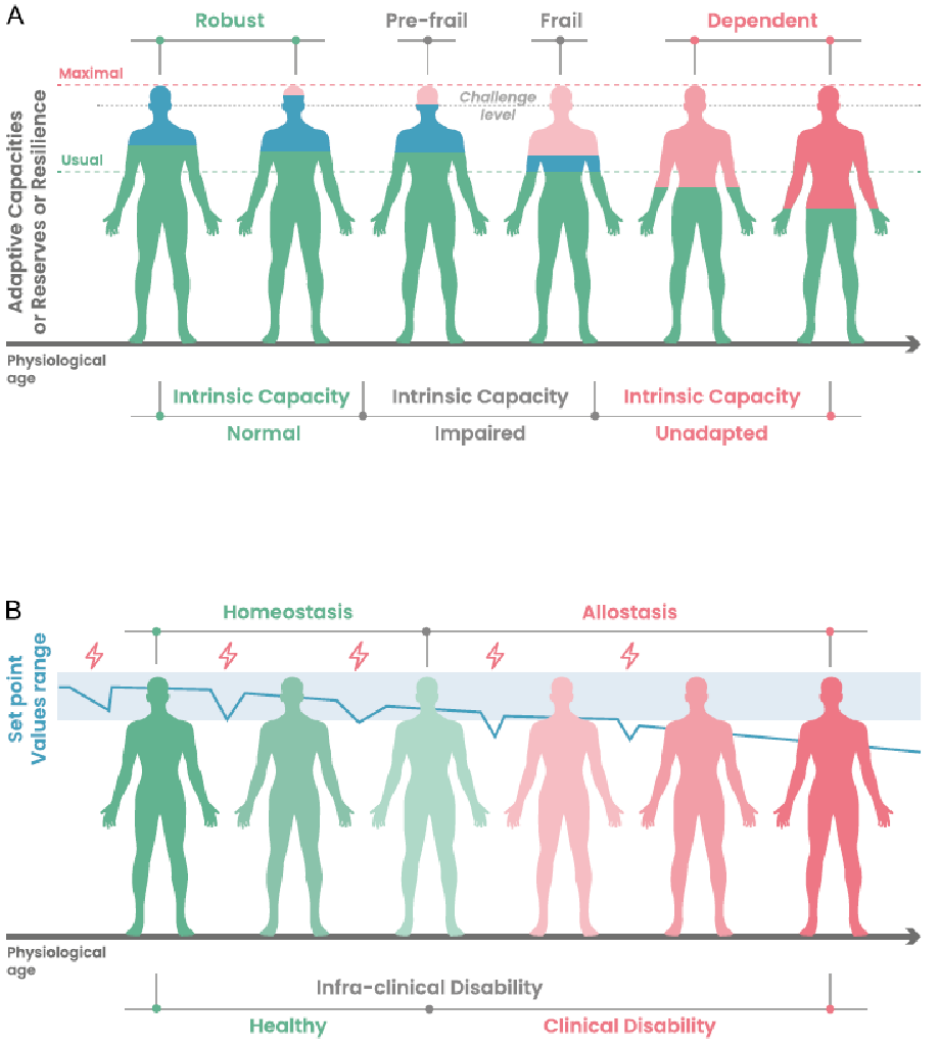
New hallmarks of ageing: a 2022 Copenhagen ageing meeting summary

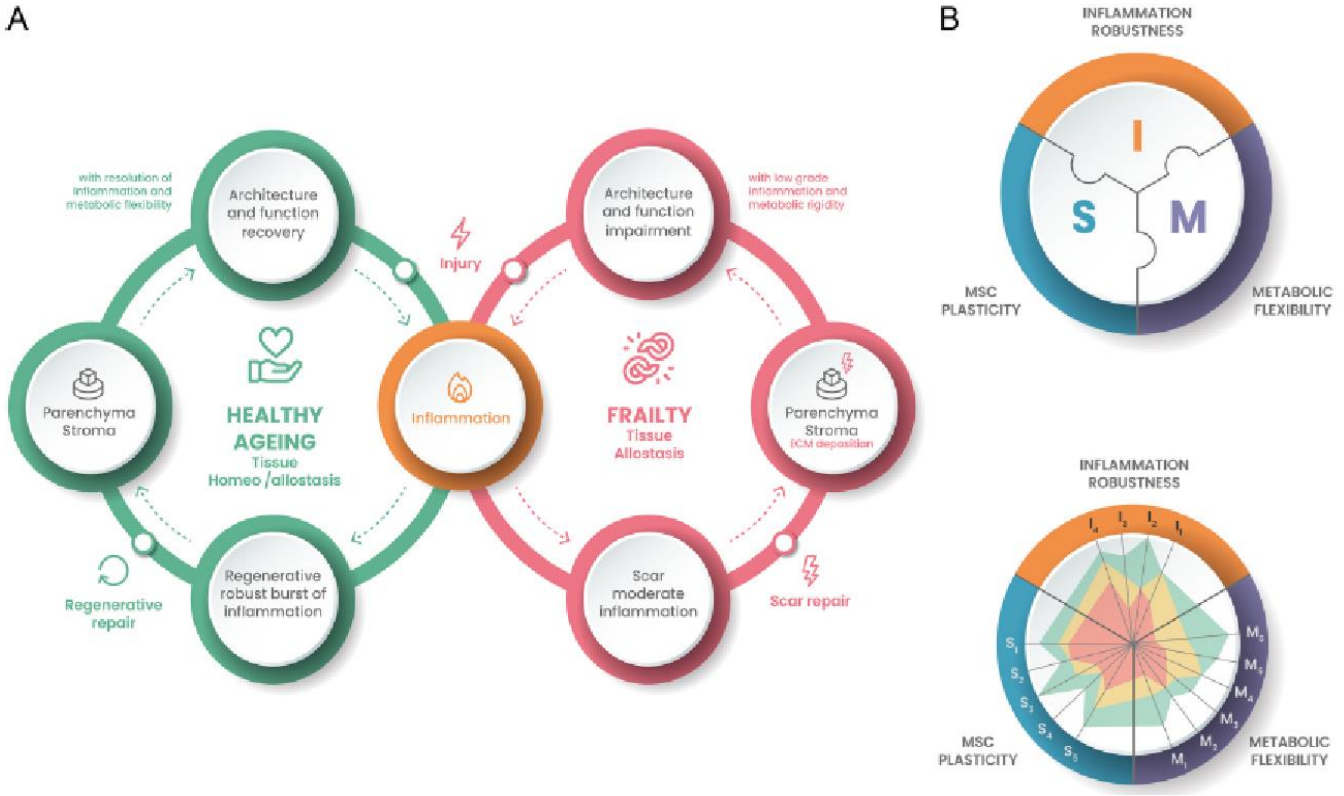
Tomas Schmauck-Medina[1,*], Adrian Molière[1,*], Sofie Lautrup[1], Jianying Zhang[1], Stefan Chlopicki[2], Helena Borland Madsen[3], Shuqin Cao[1], Casper Soendenbroe[4], Els Mansell[5,6], Mark Bitsch Vestergaard[7], Zhiquan Li[3], Yosef Shiloh[8], Patricia L. Opresko[9,18], Jean-Marc Egly[10,11], Thomas Kirkwood[3,12], Eric Verdin[13], Vilhelm A. Bohr[3,14], Lynne S. Cox[15], Tinna Stevnsner[16], Lene Juel Rasmussen[3], Evandro F. Fang[1,17]

Geroscience: The intersection of basic aging biology, chronic disease, and health



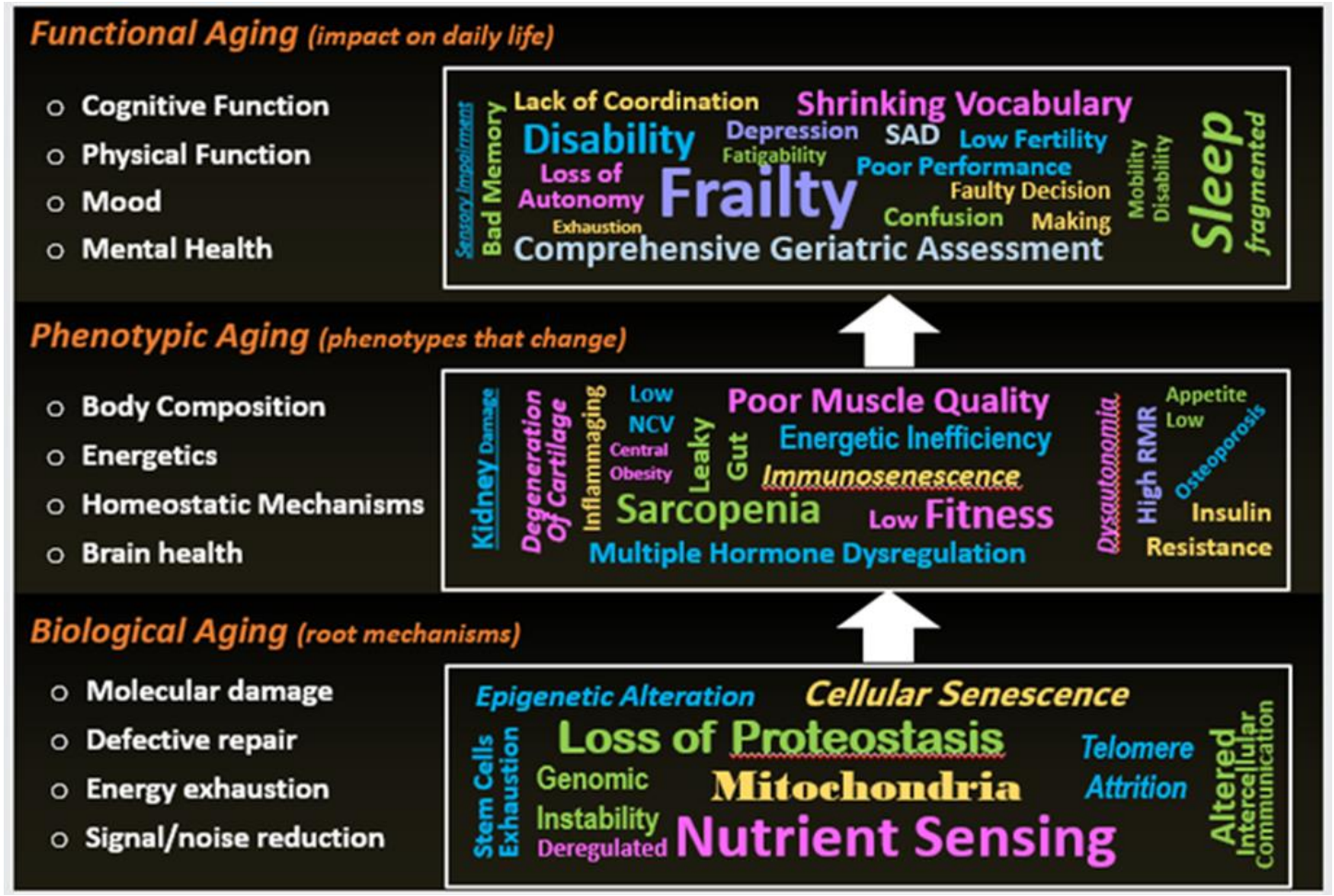
Geroscience opens the way of gerophysiology





Ageing Research Reviews 73 (2022) 101537

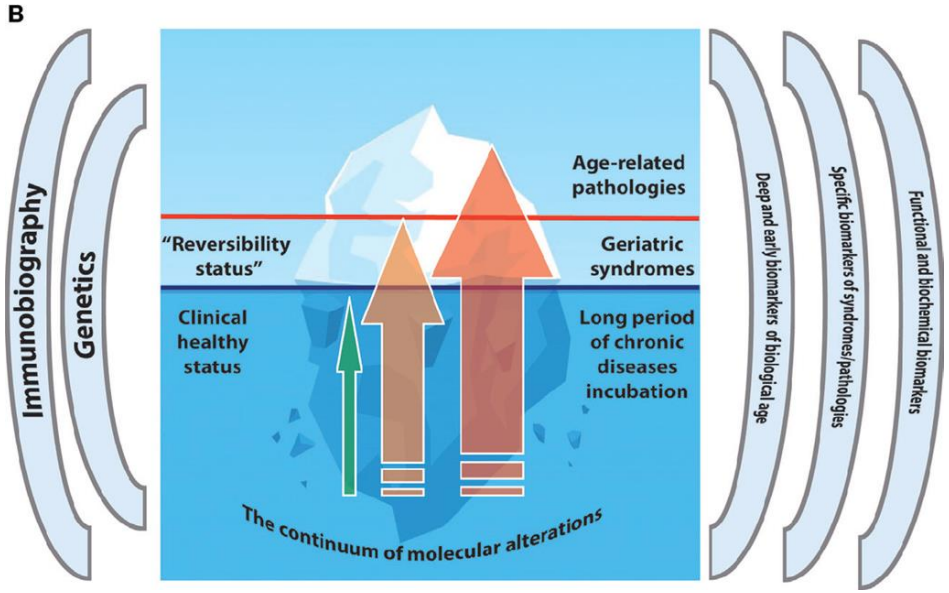
Geroscience : biomarkers of aging and of aging-related diseases



(**Clinical**) Time to incidence of any age-related disease:
MI, stroke, CHF, cancer*, MCI/dementia, or death.

(**Functional**) Decline in mobility or cognitive function.

(**Biological**) Change in biomarkers of aging.



Biomarkers of Longevity

Analytical Report

Current State, Challenges and Opportunities
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AGING ANALYTICS AGENCY

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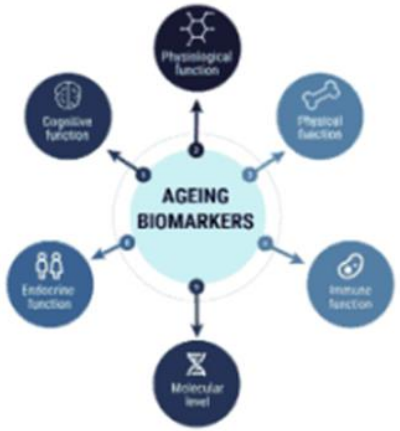


www.aginganalytics.com

Ageing Research Reviews 59 (2020) 101027

Contents lists available at ScienceDirect

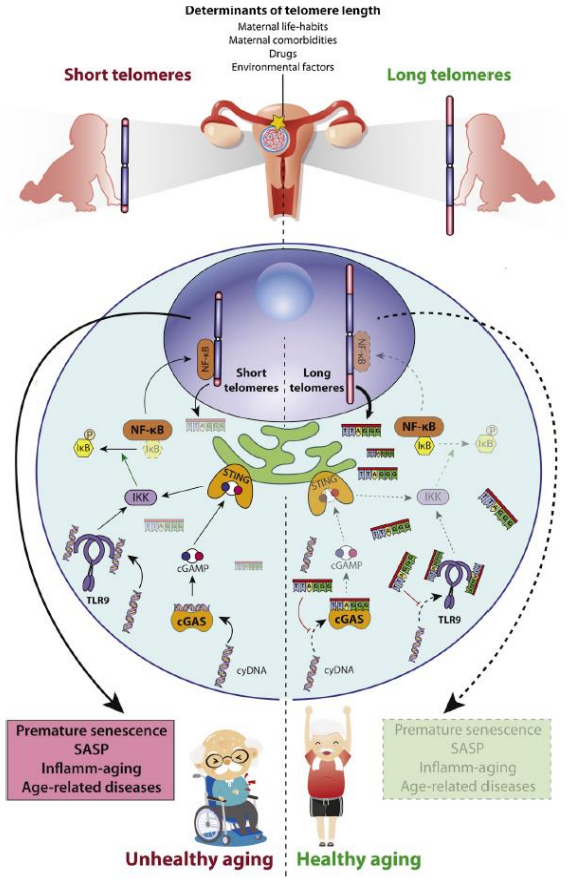
Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review

Exploiting the telomere machinery to put the brakes on inflamm-aging

Massimiliano Bonafè[a], Jacopo Sabbatinelli[b,*], Fabiola Olivieri[b,c]



Telomeres are the genomic portions at the ends of linear chromosomes (TTAGGG repeats). DNA replication and a plethora of stress conditions (oxidative stress) result in the generation of chromosomes with progressively shortened telomeres. Following telomere dysfunction, cells may activate DNA damage response (DDR) a proinflammatory response or undergo cell death by apoptosis or autophagy.

Ageing Research Reviews 50 (2019) 27–42

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review

The telomere world and aging: Analytical challenges and future perspectives

Emanuela Mensà[a], Silvia Latini[a], Deborah Ramini[a], Gianluca Storci[b,c], Massimiliano Bonafè[b,c,d], Fabiola Olivieri[a,e,*]

DIABETICMedicine

Article: Genetics

Leukocyte telomere length is associated with complications of Type 2 diabetes mellitus

R. Testa[1], F. Olivieri*†[1], C. Sirolla‡, L. Spazzafumo‡, M. R. Rippo*, M. Marra, A. R. Bonfigli, A. Ceriello§, R. Antonicelli¶, C. Franceschi**, C. Castellucci*, I. Testa and A. D. Procopio*†

www.impactjournals.com/oncotarget/ Oncotarget, Advance Publications 2016

Leukocyte telomere length and mortality risk in patients with type 2 diabetes

Anna Rita Bonfigli[1], Liana Spazzafumo[2], Francesco Prattichizzo[3], Massimiliano Bonafè[4], Emanuela Mensà[5], Luigina Micolucci[6], Angelica Giuliani[6], Paolo Fabbietti[2], Roberto Testa[7], Massimo Boemi[8], Fabrizia Lattanzio[1] and Fabiola Olivieri[5,6]

JAMA Internal Medicine | Original Investigation

Association of Telomere Length With Risk of Disease and Mortality

Carolin V. Schneider, MD; Kai Markus Schneider, MD, PhD; Alexander Teumer, PhD; Karl Lenhard Rudolph, MD; Daniel Hartmann, MD, PhD; Daniel J. Rader, MD; Pavel Strnad, MD

JAMA Intern Med. 2022;182(3):291-300. doi:10.1001/jamainternmed.2021.7804
Published online January 18, 2022.

Key Points

Question Is telomere length associated with mortality and development of specific diseases?

Findings In this cohort study, UK Biobank data from more than 450 000 individuals found that reduced baseline leukocyte telomere length was associated with increased overall and various disease-specific mortalities. The study identified more than 200 disorders that were significantly overrepresented or underrepresented in participants with shorter leukocyte telomere length.

Meaning The study findings suggest the relevance of telomere shortening for several diseases and warrant further mechanistic and therapeutic studies.

Figure 1. Association of Overall and Cause-Specific Mortality With Leukocyte Telomere Shortening Adjusted for Age, Sex, Body Mass Index (BMI), and Ethnicity

Figure 3. Most Overrepresented Phecodes in Patients With Shorter Telomeres

Figure 4. Association Between Telomere Length and the Top 25 Cancers That Lead to Death, Sorted by Descending Hazard Ratio (HR), and Adjusted for Age, Sex, Body Mass Index (BMI), and Ethnicity

Top 25 cancers leading to death (*ICD-10* code)	HR (95% CI)	*P* value
Overall mortality of malignant neoplasms (C00-99)	1.02 (1.00-1.03)	.04
Lymphoid leukemia (C91)	1.64 (1.43-1.88)	<.001
Myeloid leukemia (C92)	1.34 (1.20-1.49)	<.001
Non-Hodgkin lymphoma (C85)	1.20 (1.06-1.36)	.01
Nonfollicular lymphoma (C83)	1.18 (1.02-1.36)	.03
Malignant neoplasm of esophagus (C15)	1.12 (1.05-1.20)	<.001
Malignant neoplasm of bladder (C67)	1.10 (0.99-1.22)	.07
Malignant neoplasm of prostate (C61)	1.07 (1.00-1.14)	.04
Malignant neoplasm of liver and bile ducts (C22)	1.06 (0.97-1.16)	.20
Hepatocellular carcinoma (22.0)	1.13 (0.99-1.29)	.08
Malignant neoplasm of pancreas (C25)	1.02 (0.97-1.08)	.43
Malignant neoplasm of colon (C18)	1.02 (0.95-1.10)	.52
Cancer of unknown origin (C80)	1.02 (0.95-1.10)	.62
Malignant neoplasm of the lung (C34)	1.02 (0.98-1.06)	.41
Malignant neoplasm of stomach (C16)	1.01 (0.91-1.11)	.88
Malignant neoplasm of breast (C50)	0.98 (0.92-1.03)	.38
Malignant neoplasm of rectum (C20)	0.97 (0.86-1.08)	.57
Malignant neoplasm of intestinal tract (C26)	0.97 (0.86-1.09)	.61
Malignant neoplasm of rectosigmoid (C19)	0.96 (0.86-1.06)	.40
Malignant neoplasm of kidney (C64)	0.96 (0.87-1.07)	.45
Malignant neoplasm of ovary (C56)	0.94 (0.86-1.02)	.12
Multiple myeloma (C90)	0.92 (0.82-1.02)	.10
Malignant neoplasm of uterus (C54)	0.88 (0.76-1.01)	.06
Malignant neoplasm of other connective and soft tissue (C49)	0.88 (0.74-1.04)	.13
Malignant neoplasm of brain (C71)	0.87 (0.81-0.94)	<.001
Mesothelioma (C45)	0.87 (0.78-0.96)	.01
Melanoma (C43)	0.80 (0.71-0.89)	<.001

Hazard ratios per *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* code were generated from competing risk regression models, accounting for the risk of death through other causes. The HRs (95% CI) per SD decrease of telomere length are shown. BMI is calculated as weight in kilograms divided by height in meters squared.

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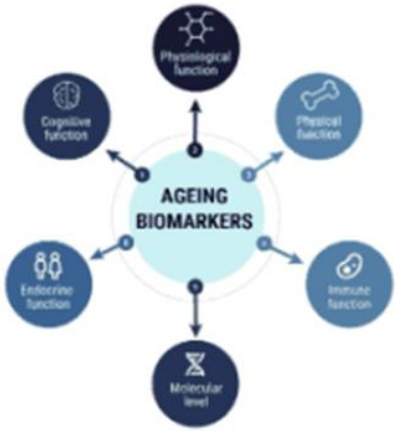
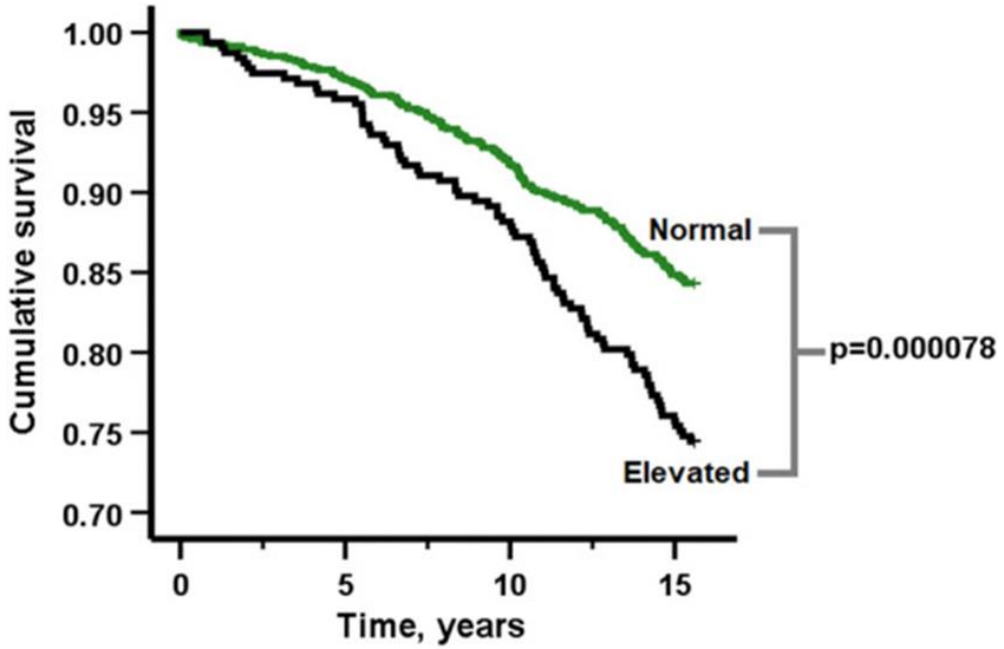




Kanene et al., 2020

The estimated survival probabilities according to the baseline cf-DNA level divided into two groups. Individuals in the highest gender-wise cf-DNA quartile (n = 313, 80 [26%] deceased) were included to the group of "elevated cf-DNA levels" (black line) and all the other individuals (n = 944, 148 [16%] deceased) in "normal cf-DNA levels" (green line)

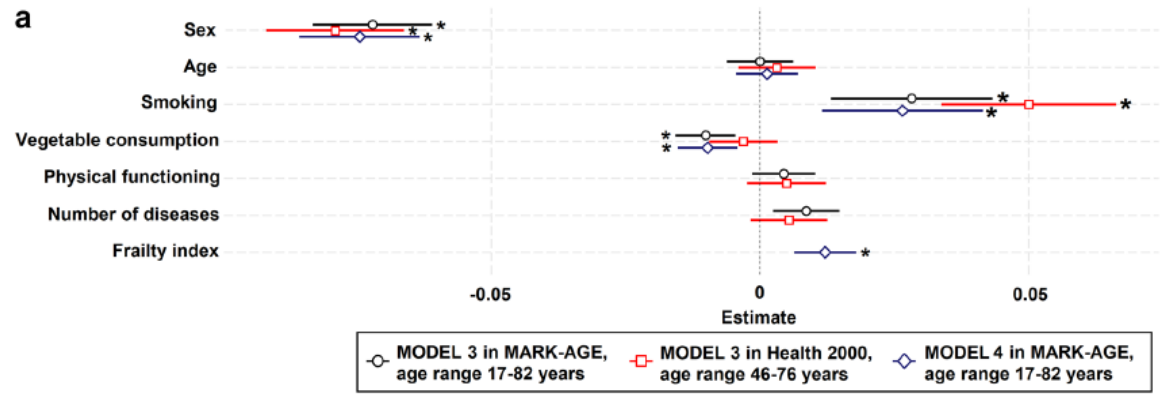
GeroScience
https://doi.org/10.1007/s11357-022-00590-8

ORIGINAL ARTICLE

Circulating cell-free DNA in health and disease — the relationship to health behaviours, ageing phenotypes and metabolomics

Laura Kananen · Mikko Hurme · Alexander Bürkle · Maria Moreno-Villanueva · Jürgen Bernhardt · Florence Debacq-Chainiaux · Beatrix Grubeck-Loebenstein · Marco Malavolta · Andrea Basso · Francesco Piacenza · Sebastiano Collino · Efstathios S. Gonos · Ewa Sikora · Daniela Gradinaru · Eugene H. J. M. Jansen · Martijn E. T. Dollé · Michel Salmon · Wolfgang Stuetz · Daniela Weber · Tilman Grune · Nicolle Breusing · Andreas Simm · Miriam Capri · Claudio Franceschi · Eline Slagboom · Duncan Talbot · Claude Libert · Jani Raitanen · Seppo Koskinen · Tommi Härkänen · Sari Stenholm · Mika Ala-Korpela · Terho Lehtimäki · Olli T. Raitakari · Olavi Ukkola · Mika Kähönen · Marja Jylhä · Juulia Jylhävä

GeroScience



The relationship of cf-DNA levels to sex, age, smoking, vegetable consumption,physical functioning, number of diseases and frailty in the MARKAGE and Health 2000 cohorts.

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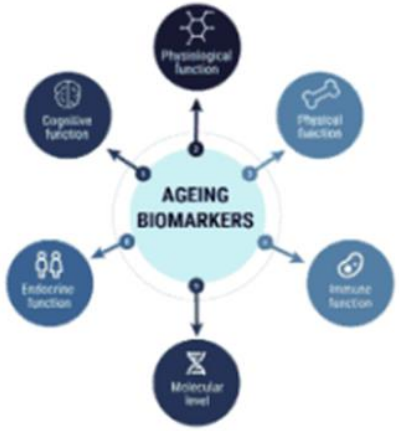

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Ageing Research Reviews 70 (2021) 101374

Contents lists available at ScienceDirect

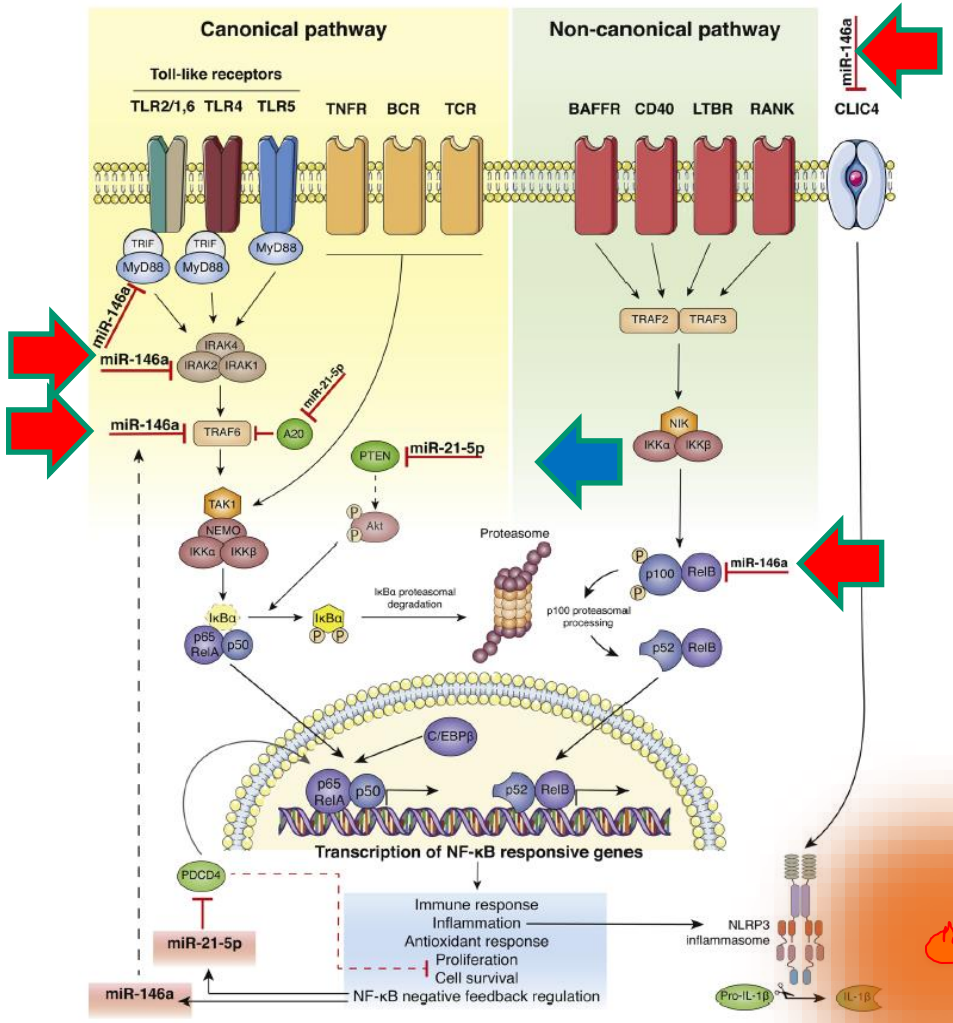
Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

miR-21 and miR-146a: The microRNAs of inflammaging and age-related diseases

Fabiola Olivieri [a,b,*], Francesco Prattichizzo [c], Angelica Giuliani [a], Giulia Matacchione [a], Maria Rita Rippo [a], Jacopo Sabbatinelli [a,*], Massimiliano Bonafè [d]

MiR-21 and miR-146 can modulate a number of molecular targets belonging to the NF-Kb pathway activation. The NF-κB signaling pathway is the most relevant proinflammatory signaling response pathways implicated in aging. Increasing evidence strongly suggest that the activation or inhibition of NF-κB can induce or reverse respectively the main features of aged organisms.



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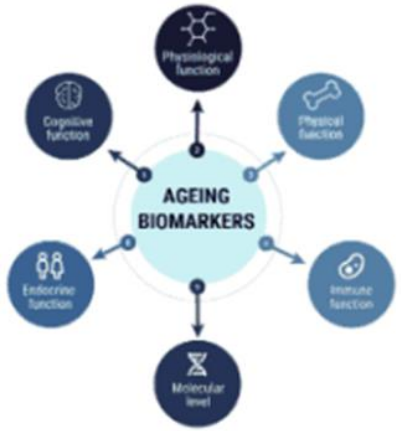


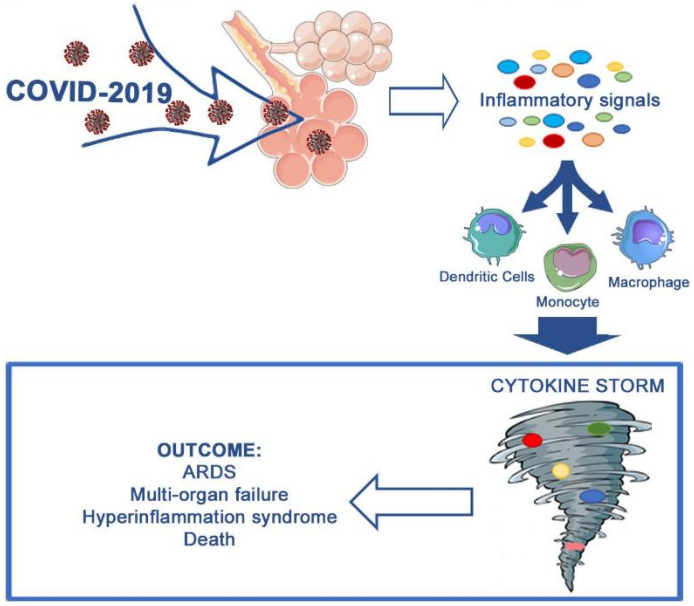
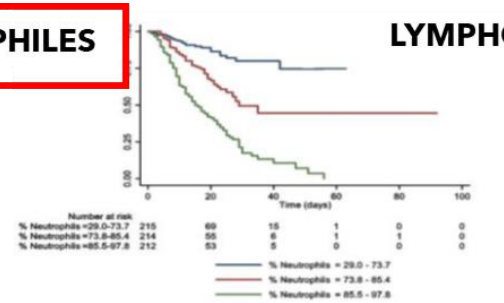


Table 1
Sample description.

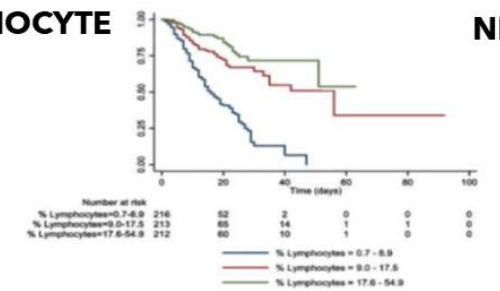
	Total n = 641	Survived n = 421	Deceased n = 220	p
Age, mean ± sd	86.6 ± 6.8	85.6 ± 7.2	88.5 ± 5.5	< 0.001
Male gender, n (%)	266 (41.5%)	159 (37.8%)	107 (48.6%)	0.008

NEUTROPHILES



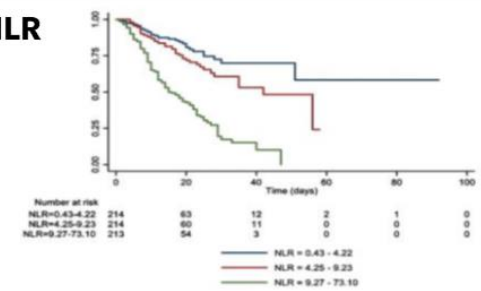
Log-rank test for equality of survivor functions:
χ^2=116.76; p<0.001

LYMPHOCYTE



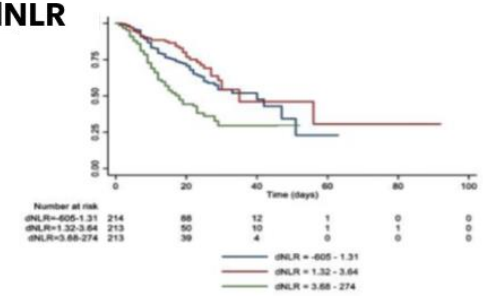
Log-rank test for equality of survivor functions:
χ^2=102.67; p<0.001

NLR



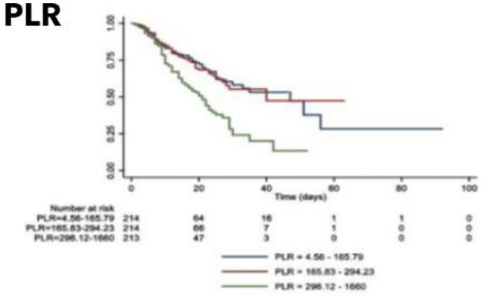
Log-rank test for equality of survivor functions:
χ^2=97.47; p<0.001

dNLR



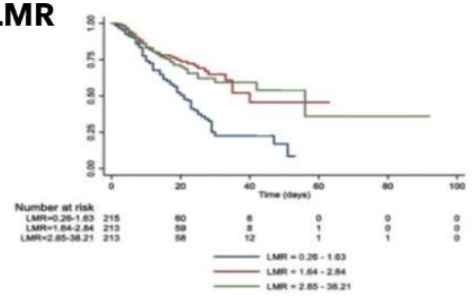
Log-rank test for equality of survivor functions:
χ^2=43.72; p<0.001

PLR



Log-rank test for equality of survivor functions:
χ^2=26.05; p<0.001

LMR



Log-rank test for equality of survivor functions:
χ^2=31.50; p<0.001

Mechanisms of Ageing and Development 204 (2022) 111674

Contents lists available at ScienceDirect

Mechanisms of Ageing and Development

journal homepage: www.elsevier.com/locate/mechagedev

Routine laboratory parameters, including complete blood count, predict COVID-19 in-hospital mortality in geriatric patients

Fabiola Olivieri [a,b,1], Jacopo Sabbatinelli [a,c,1], Anna Rita Bonfigli [d,*], Riccardo Sarzani [a,e], Piero Giordano [e], Antonio Cherubini [f], Roberto Antonicelli [g], Yuri Rosati [h], Simona Del Prete [i], Mirko Di Rosa [j], Andrea Corsonello [j,k], Roberta Galeazzi [l], Antonio Domenico Procopio [a,l], Fabrizia Lattanzio [d]

Biomarkers of Longevity

Analytical Report

Current State, Challenges and Opportunities
Landscape Overview 2019

AGING ANALYTICS AGENCY

Selected Biomarkers List

1. Gait (Walking) Speed
2. Timed Get Up and Go
3. Chair Rising
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5. Standing Balance
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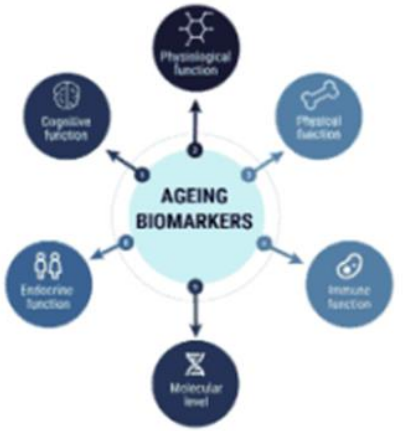
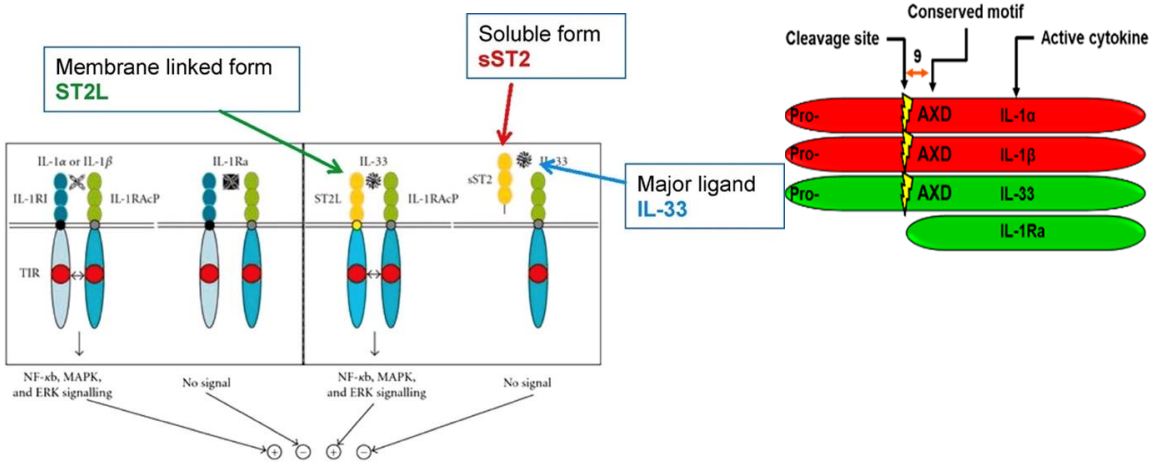


www.aginganalytics.com

IL-1 family cytokines



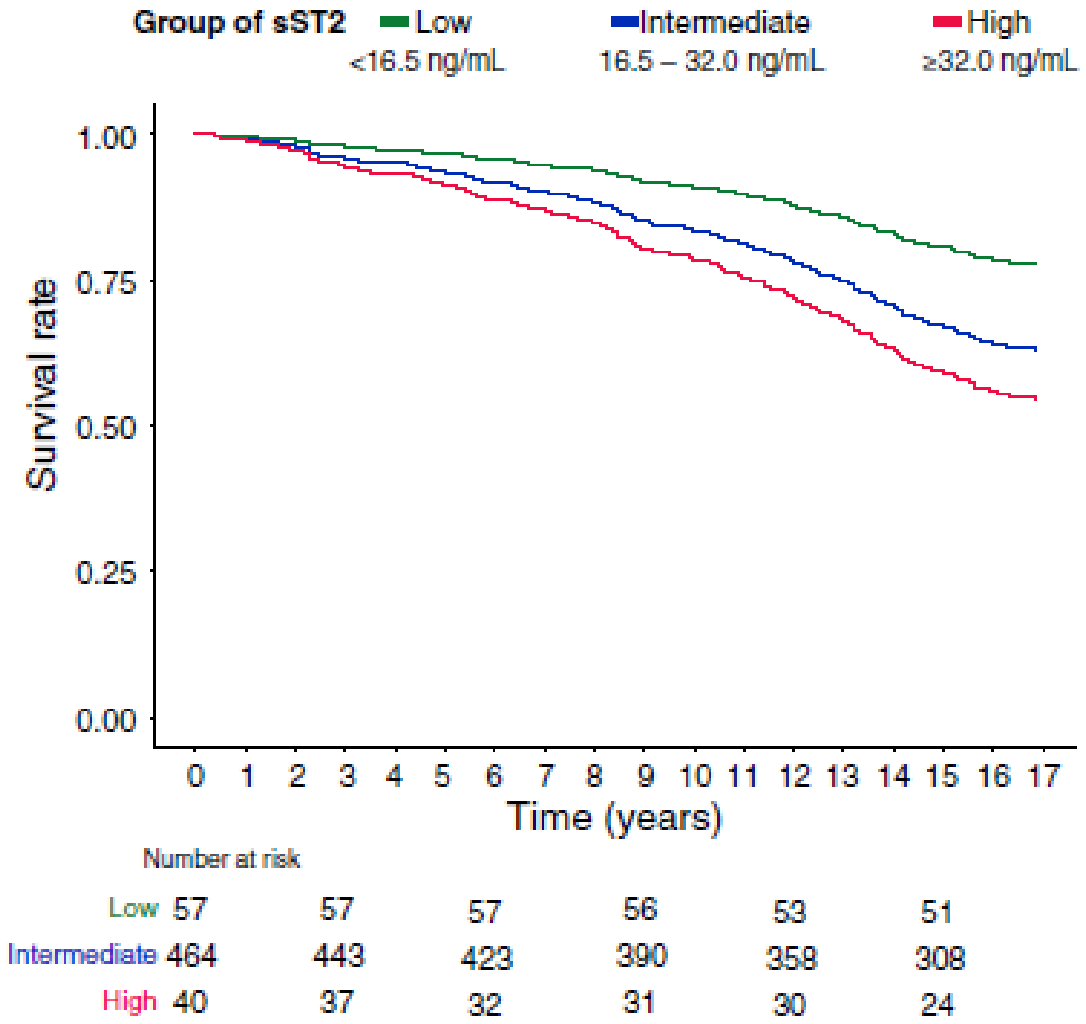
Sabbatinelli et al. Cardiovascular Diabetology (2022) 21:180
https://doi.org/10.1186/s12933-022-01616-3

Cardiovascular Diabetology

RESEARCH Open Access

Prognostic value of soluble ST2, high-sensitivity cardiac troponin, and NT-proBNP in type 2 diabetes: a 15-year retrospective study

Jacopo Sabbatinelli[1,2*†], Angelica Giuliani[1†], Anna Rita Bonfigli[3], Deborah Ramini[4], Giulia Matacchione[1], Carla Campolucci[2], Artan Ceka[2], Elena Tortato[5], Maria Rita Rippo[1], Antonio Domenico Procopio[1,4], Marco Moretti[2*] and Fabiola Olivieri[1,4]



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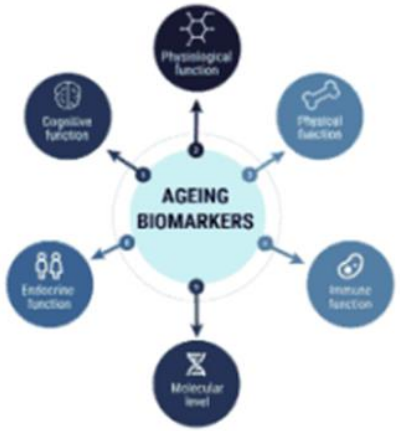
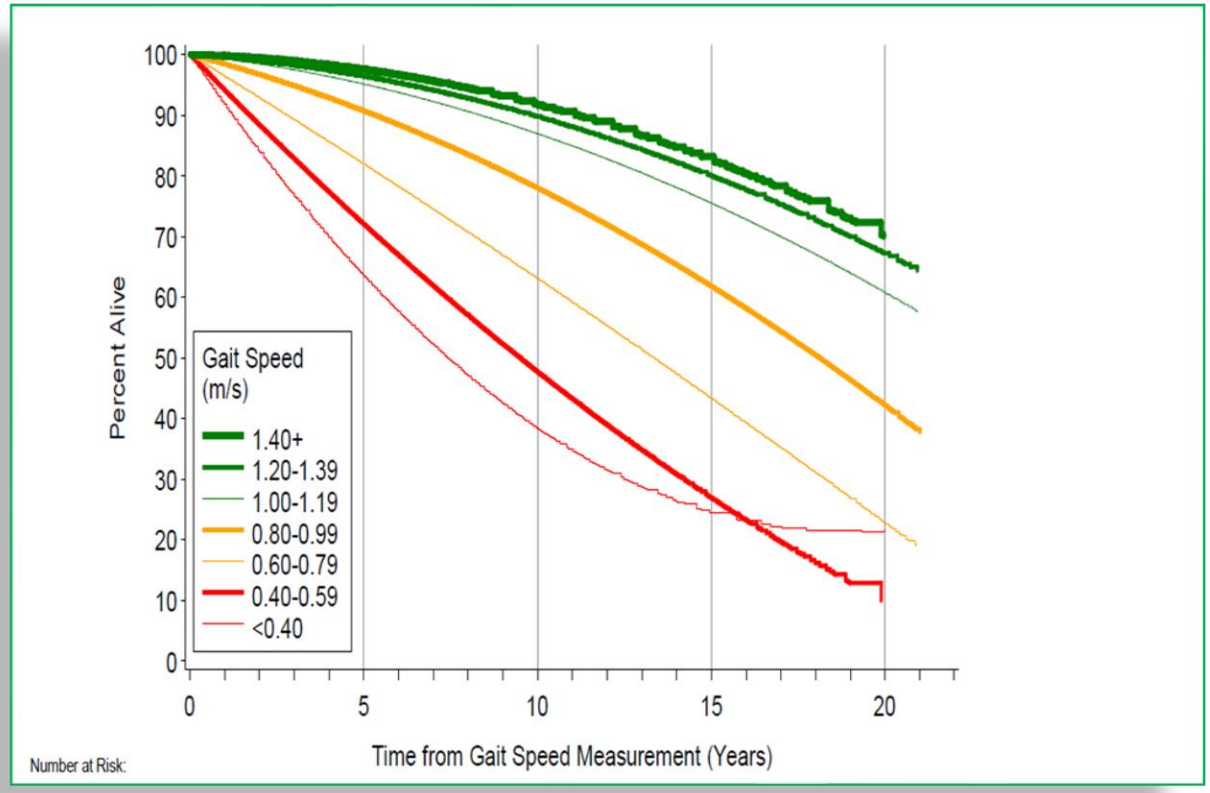
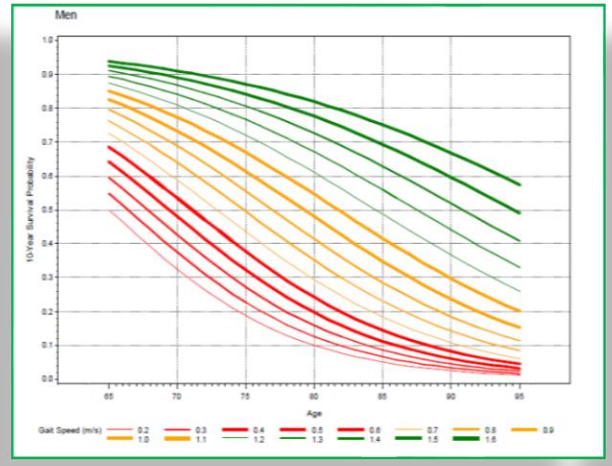
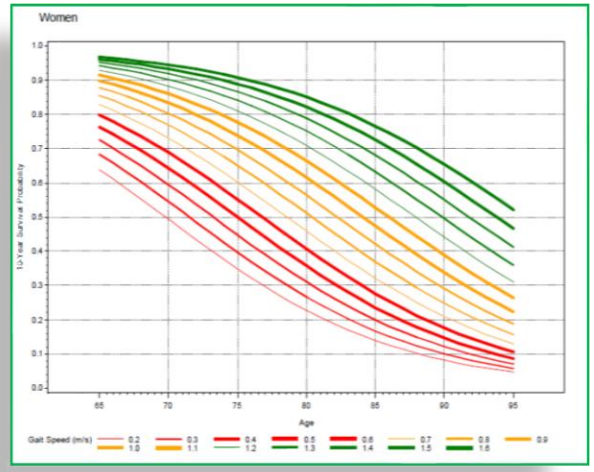


Survival According to Gait Speed Categories using pooled data from nine cohort studies

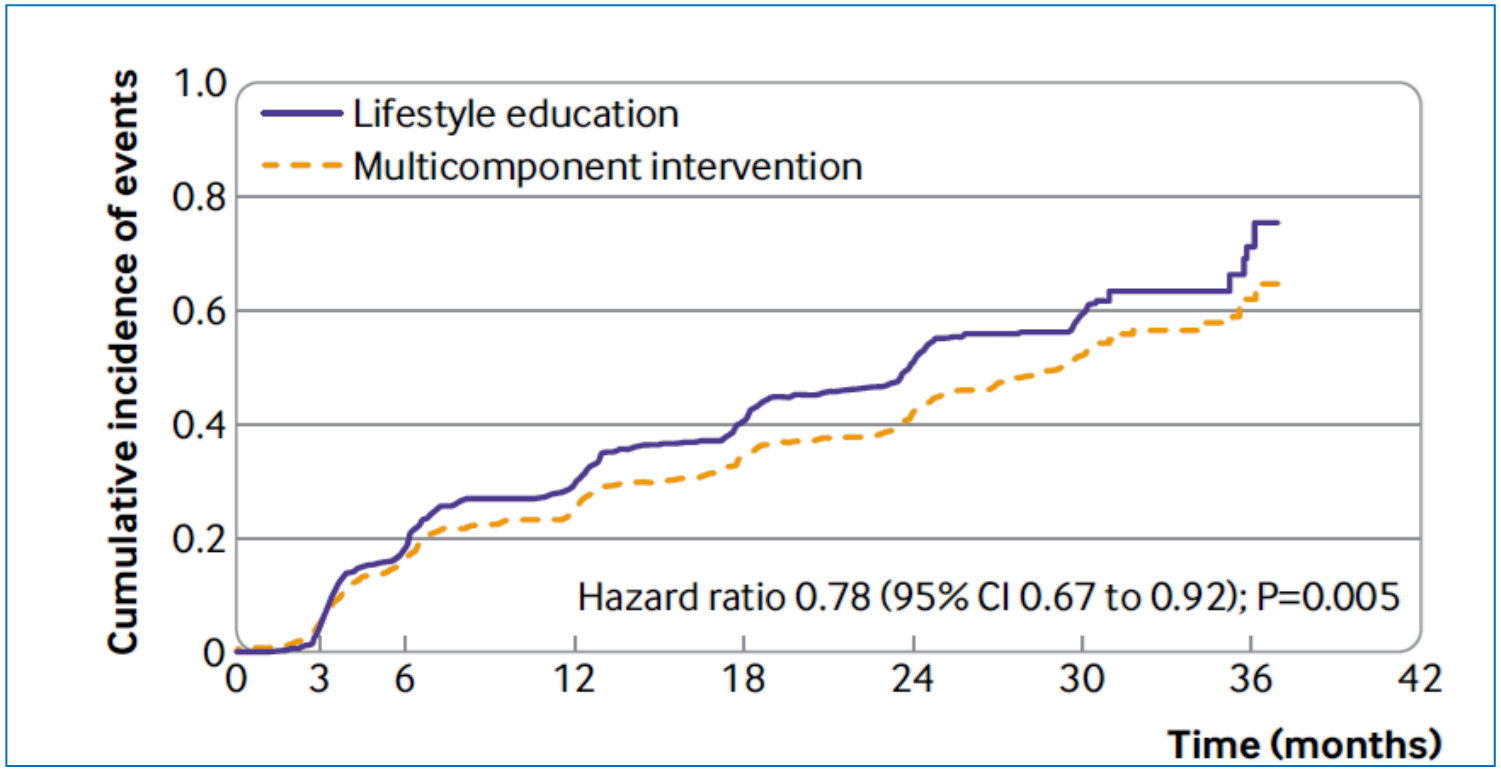






Studenski et al., JAMA 2011

SPRINT-T: efficacy of multicomponent intervention in preventing mobility disability



SPPB 3 to 7

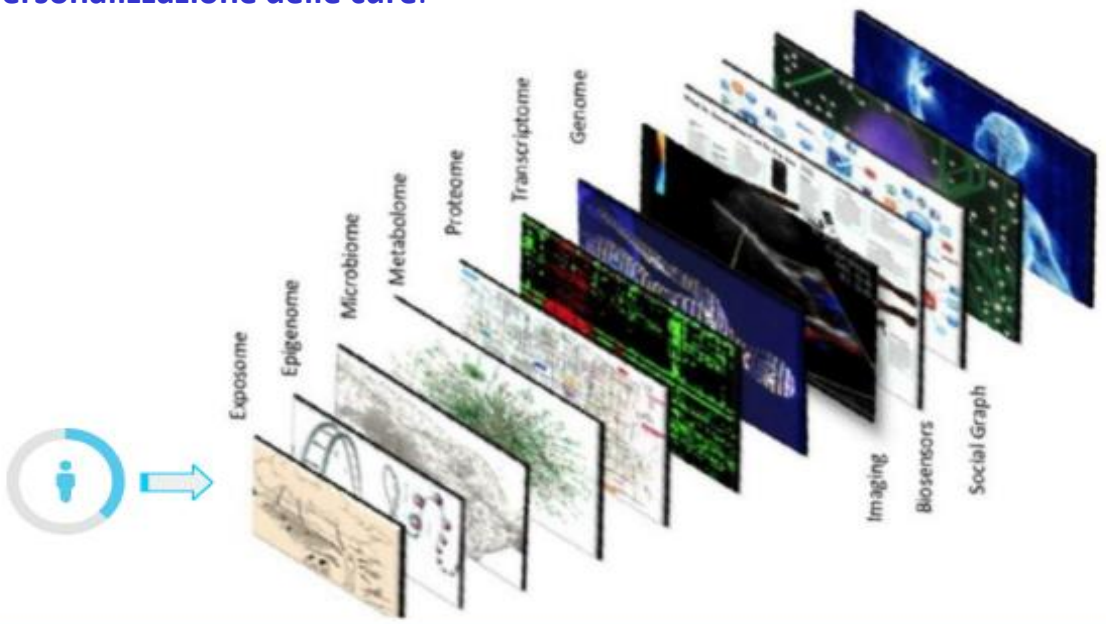
22% risk of developing mobility disability in MCI compared to HALE

Bernabei et al., BMJ 2022

Progetto I-COMET

Budget complessivo: € 5.000.000 (MEF – Ministero Salute)

Obiettivo: creazione di un **meta-dipartimento di Aging Analytics** per l'applicazione di tecniche di **Intelligenza Artificiale** finalizzate all'identificazione di **modelli predittivi di longevità**, **l'identificazione di target di trattamento** e per la **personalizzazione delle cure**.



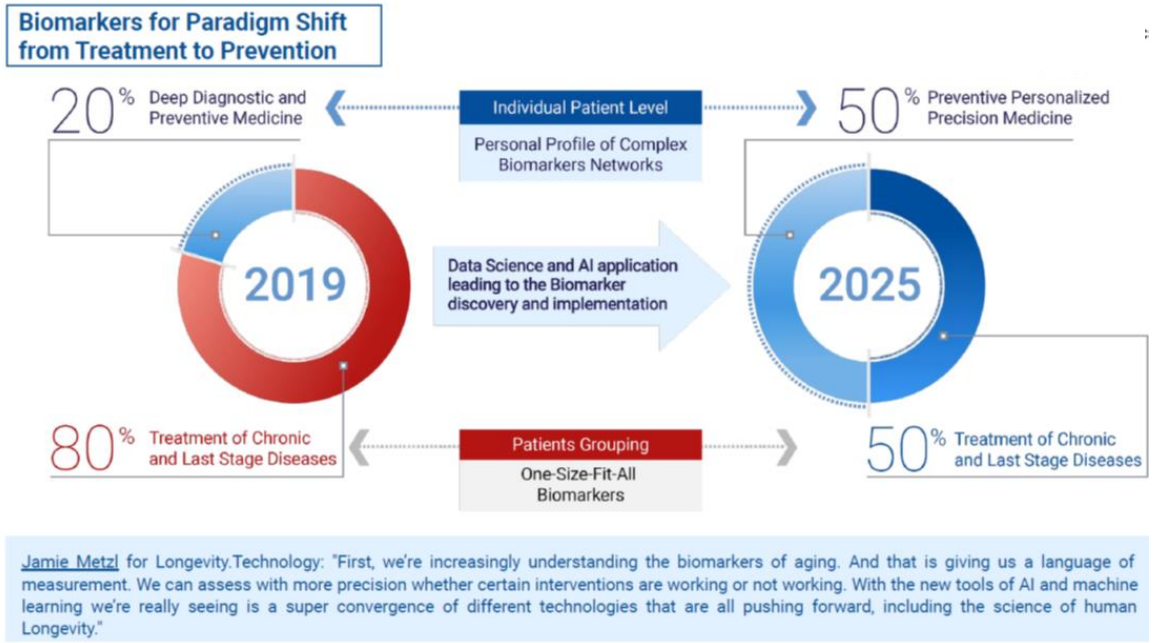
Creation of topological maps of health and disease.
"Omic" latin suffix, or "ome" = mass or many.

Rete IRCCS Aging

IRCCS COORDINATOR
Istituto Nazionale di Ricovero e Cura per Anziani - AN

IRCCS PARTNERS
Istituto Ortopedico Galeazzi - MI
Istituto Ortopedico Rizzoli - BO
Istituto di Ricerche Farmacologiche Mario Negri - MI
Ospedale Specializzato in Gastroenterologia "S. de Bellis" - Castellana - BA
Istituto Auxologico Italiano - MI
Fondazione Policlinico San Matteo - PV
Fondazione Bietti per lo studio e la ricerca in oftalmologia - RM
Fondazione Ca' Granda - Ospedale Maggiore Policlinico - MI
Fondazione Policlinico Universitario A. Gemelli - RM
Fondazione Don Carlo Gnocchi - MI
Casa Sollievo della Sofferenza - San Giovanni Rotondo - FG
Istituti Clinici Scientifici Maugeri - PV

Should I pay out of pocket to have my telomeres measured? My telomeres are shorter than average—what does that mean? Are there treatments to lengthen my telomeres?



Jamie Metzl for Longevity.Technology: "First, we're increasingly understanding the biomarkers of aging. And that is giving us a language of measurement. We can assess with more precision whether certain interventions are working or not working. With the new tools of AI and machine learning we're really seeing is a super convergence of different technologies that are all pushing forward, including the science of human Longevity."

Longevity Care Center

Category	Biomarker	Practicability of measurement according to Wagner paper	Correlated with
Physical function and anthropometry Morphological physical biomarkers	Walking speed	High	mortality
	Chair stand	High	mortality
	Standing balance	High	mortality
	Grip strength	High	mortality / CVD / cognitive impairment
	Body mass index	High	CVD / cognitive impairment / mortality
	Waist circumference	High	mortality / CVD
	Muscle mass	High	mortality
Blood-based biomarker	Inflammation IL-6, TNF-a, CRP	Moderate to high	mortality/ grip strength
	Network analysis inflammatory biomarkers	Moderate	mortality
	Glucose metabolism: HbA1c, plasma glucose	Moderate	mortality, CVD
	Adipokines	Moderate	mortality / frailty
	Thyroid hormones	Moderate	mortality / morbidity (moderate prediction)
	Vitamin D	Low	mortality / multimorbidity / cognitive impairment
	NT-proBNP Troponin	moderate	mortality / multimorbidity / cognitive impairment
Epigenetic biomarkers	DNA \ chromosomal damage	Low	frailty
	Telomere length	Low	mortality
	DNA repair	Low	-
Novel new promising biomarkers	Bilirubin	Moderate to high	CVD / CVD-related mortality
	Advanced glycation end products	low	CVD
	Metalothioneins	low	Aging Brain
	DNA methylation	low	-
	MicroRNAs	low	CVD aging