Introduction to Longevity Medicine for Physicians 2020-2021

Lecture notes

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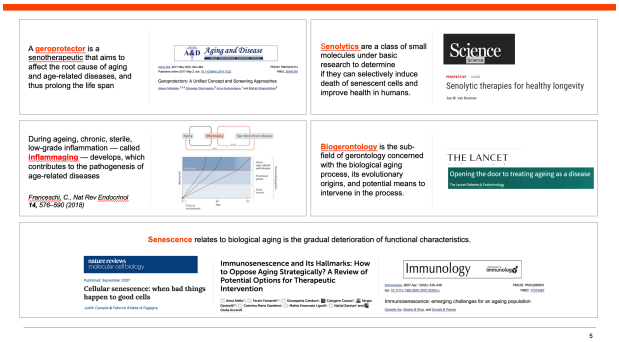
The progress in longevity medicine is rapidly accelerating. Just as any other specialty, LM has its own specific vocabulary that is crucial in order to effectively communicate with fellow colleagues. This vocabulary is essential to stay updated and follow the revolution in aging research. Knowing terms such as “aging clocks”, senolytics, NAD+ boosters, rapalogs, cellular reprogramming, gene therapy is required to navigate the literature and understand modern anti-aging technologies. Therefore, before we take a deep dive into Longevity Medicine, some key definitions need to be introduced.



Aging is an exponential decline in homeostatic capabilities, which ultimately leads to an increased risk of age-related diseases and death. Homeostasis is the ability of the organism to maintain constant internal conditions (blood acidity, oxygen saturation etc.) under the pressure of external disturbances.

Biogerontology is a sub-field of gerontology that focuses on the biological aging process, its evolutionary origins, and anti-aging interventions.

Geroprotectors are substances that can reduce the aging rate and increase the healthy lifespan. In other words, geroprotectors are drugs that target the root cause of aging and age-related diseases.

Aging biomarkers are measurable parameters that reproducibly, qualitatively and quantitatively reflect the rate of human aging.

Senescence relates to biological aging and refers to a gradual deterioration of basic function. This term is most commonly used in the context of the cellular organization level. In cells senescence is associated with the cell cycle arrest, tumour-suppressor expression and increased occurrence of phenotypic (e.g. organelles, chromatin and secretome) alterations.

Inflammaging is a chronic, aseptic, low-grade inflammation that develops during aging and reciprocally contributes to the pathogenesis of age-related diseases.

Senolytics are a class of small molecules that is being actively researched for its ability to selectively induce senescent cell death.

Recommended literature for a more in-depth study:

Campisi J, d'Adda di Fagagna F. Cellular senescence: when bad things happen to good cells. Nat Rev Mol Cell Biol. 2007 Sep;8(9):729-40. doi: 10.1038/nrm2233. PMID: 17667954.

Aw D, Silva AB, Palmer DB. Immunosenescence: emerging challenges for an ageing population. Immunology. 2007 Apr; 120(4):435-46. doi: 10.1111/j.1365-2567.2007.02555. x. Epub 2007 Feb 15. PMID: 17313487; PMCID: PMC2265901.

Opening the door to treating ageing as a disease. Lancet Diabetes Endocrinol. 2018 Aug;6(8):587. doi: 10.1016/S2213-8587(18)30214-6

van Deursen J. M. (2014). The role of senescent cells in ageing. *Nature*, *509*(7501), 439–446. https://doi.org/10.1038/nature13193

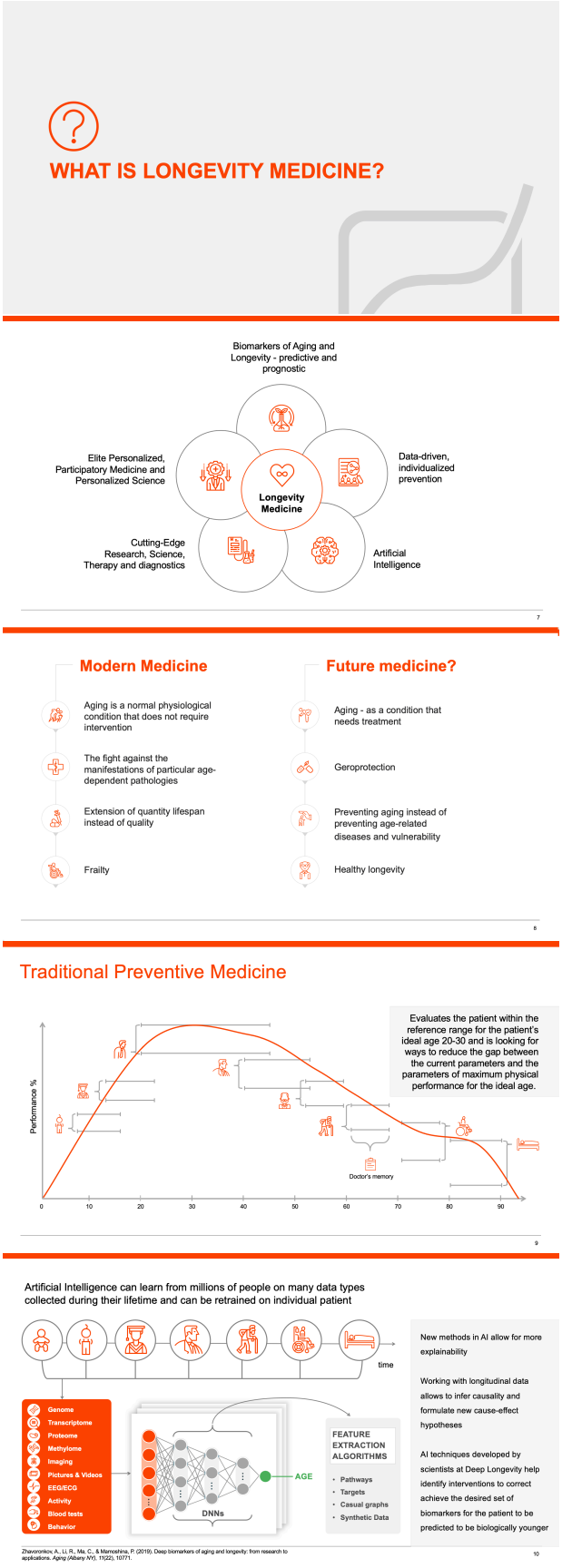
López-Otin C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. Cell. 2013; 153:1194–1217

Not open-source materials*

Franceschi, C., Garagnani, P., Parini, P. et al. Inflammaging: a new immune–metabolic viewpoint for age-related diseases. Nat Rev Endocrinol 14, 576–590 (2018). https://doi.org/10.1038/s41574-018-0059-4*

Campisi J, d'Adda di Fagagna F. Cellular senescence: when bad things happen to good cells. Nat Rev Mol Cell Biol. 2007 Sep;8(9):729-40. doi: 10.1038/nrm2233. PMID: 17667954. *

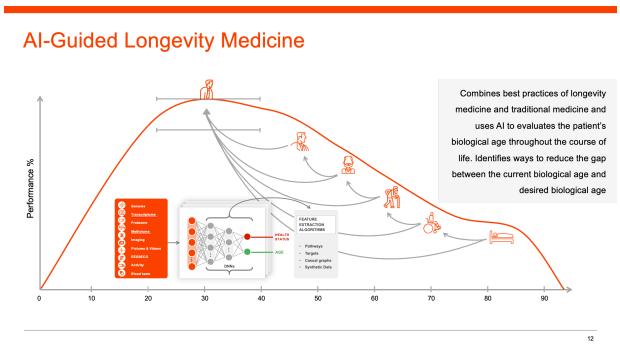
What is longevity medicine?



Modern medicine does not focus on preventing or reversing aging, which is the primary cause of multiple chronic diseases collectively called “age-related diseases”. This group is comprised of cardiovascular, oncologic, metabolic, neurodegenerative pathologies, some more harmful than others. The commonly used symptomatic approach in age-related disease treatment is possible only once the disease has already manifested itself. Thus, the period of senility, characterized by a steep drop in the quality of life, is prolonged. By targeting the cause of these diseases – aging – the future medicine can significantly delay their onset, prevent chronification and relapse. Overall, aging-focused therapies promise to extend the healthy period of life.

Traditional medicine, even at its advanced level of precision, evaluates the patient according to the biological parameters typical for their age group and aims to fit the patient within their age group reference ranges. These reference ranges represent population means with no respect for individual differences. In contrast, longevity (preventive) medicine is guided by AI and allows for a personalized approach. Unlike the conventional statistic-driven approach, it focuses not on the gap between the current state of the patient and the “normal” state for an age group, but on the gap between the patient and their own maximum of physical fitness. Not only this, but the AI-driven approach identifies the ways to bridge this gap.

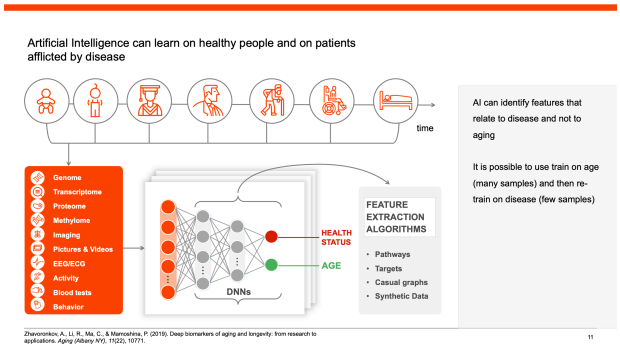
The role of AI in contemporary medicine cannot be underestimated. New methods in AI add extra explainability to the standard clinical tests. Working with longitudinal data allows to infer causality and formulate new cause-effect hypotheses. AI techniques help identify the interventions to achieve the desired set of biomarkers for a patient to become biologically younger. AI systems that were trained with a proper procedure can be disease-relevant, which means they may be able to tell a healthy aging process from a particular disease and pinpoint the molecular features associated with it.

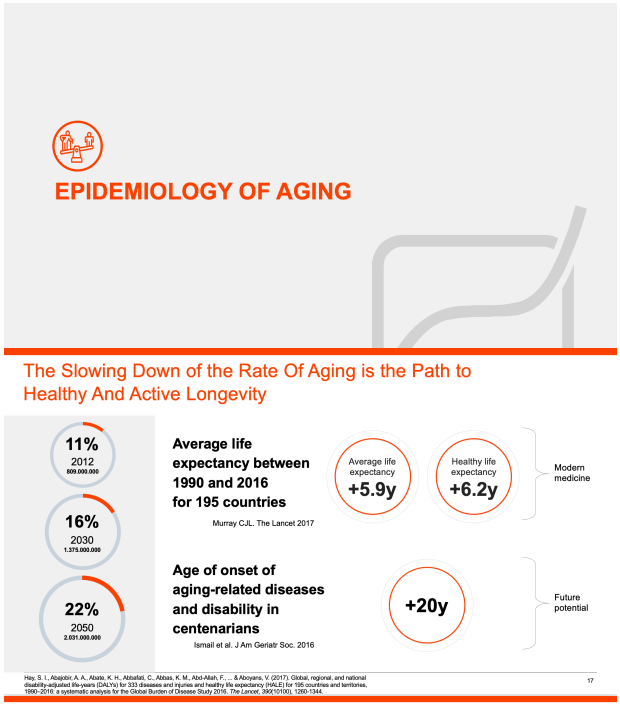


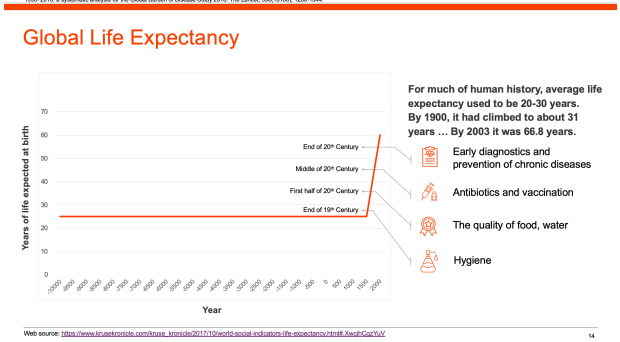
Recommended literature for a more in-depth study:

Zhavoronkov, A., Li, R., Ma, C., & Mamoshina, P. (2019). Deep biomarkers of aging and longevity: from research to applications. *Aging (Albany NY)*, *11*(22), 10771.

Epidemiology of aging



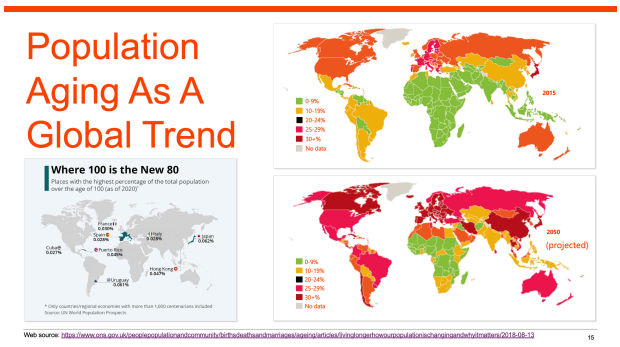


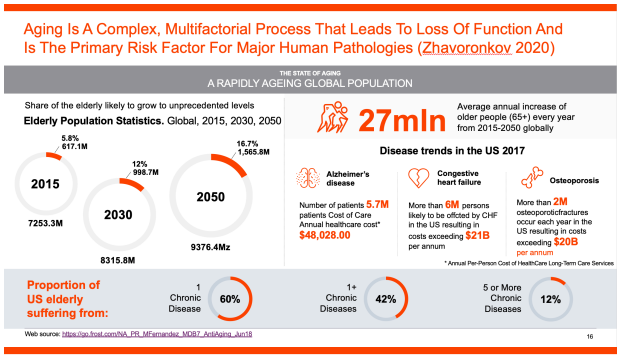


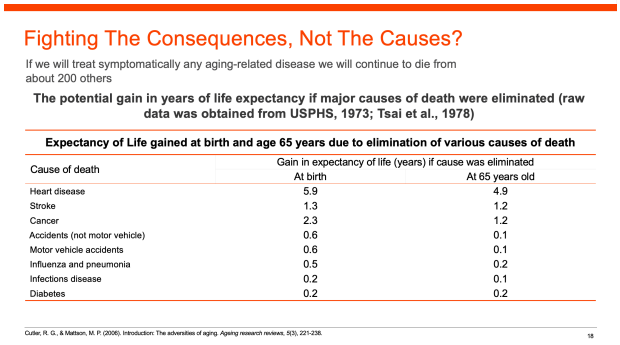
In the pre-industrial era a person's life expectancy at birth was below 40 years. Disruptive events such as hunger, infectious diseases, wars and child mortality reduced the likelihood of living up to old age. At the turn of the last century new medical technologies emerged: vaccination, sanitary regulations, antibiotics, methods of early diagnostics. Coincidentally, food and water supply quality improved significantly. As a result, a sharp increase in the life expectancy and the duration of a healthy lifespan occurred on a global scale. Human lifespan rose by 6 years. Consequently, the proportion of the elderly population started creeping up in the developed countries. Soon this trend will affect most other regions of the world.

This is the greatest achievement of modern civilization. However, aging contributes to virtually all chronic noncommunicable diseases that currently affect tens of millions of people in the US alone. Rising prevalence of the elderly, i.e. less productive and/or chronically ill individuals, place a heavy burden on the economies worldwide.

Studies of centenarians who are known to have slower aging rate show that chronic diseases come to them 20 years later on average. This proves that longevity medicine has significant potential to prolong healthy longevity while focusing on decelerating aging.
Calculations demonstrate the limitations of the current healthcare model, which focuses on partially preventing, but mostly on managing chronic diseases and their symptoms. Importantly,







even a complete elimination of any single cause of death (cancer, heart attack, stroke) would increase human lifespan by only a few years, as they would be replaced by another bottleneck. The real solution to the healthy longevity problem is impossible while hunting down particular manifestations of aging — we need to strike at its root.

Recommended literature for a more in-depth study:

H. Beltrán-Sánchez, E. M. Crimmins & C. E. Finch (2012) Early cohort mortality predicts the rate of aging in the cohort: a historical analysis, Journal of Developmental Origins of Health and Disease, 3(5), 380-386. https://doi.org/10.1017/S2040174412000281.

Web-source:

https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/ageing/articles/livinglongerhowourpopulationischangingandwhyitmatters/2018-08-13

Web-source:

https://go.frost.com/NA_PR_MFernandez_MDB7_AntiAging_Jun18

Web-source:

https://www.rand.org/well-being/social-and-behavioral-policy/centers/aging/rsi/demography.html

Not open-source materials*

Ferrucci, L., Giallauria, F., & Guralnik, J. M. (2008). Epidemiology of aging. Radiologic clinics of North America, 46(4), 643–v. https://doi.org/10.1016/j.rcl.2008.07.005

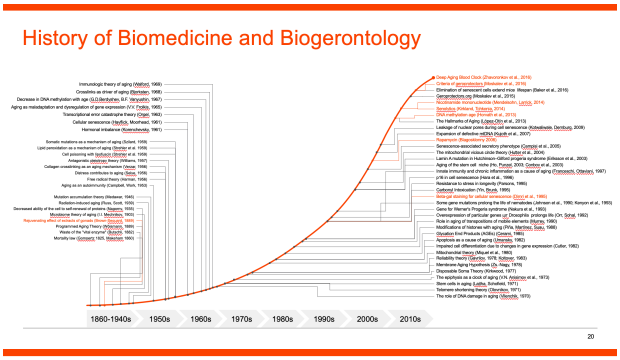
M.J. Divo, C.H. Martinez, D.M. Mannino, (2014) Ageing and the epidemiology of multimorbidity.European Respiratory Journal, 44 (4) 1055-1068; DOI: 10.1183/09031936.00059814

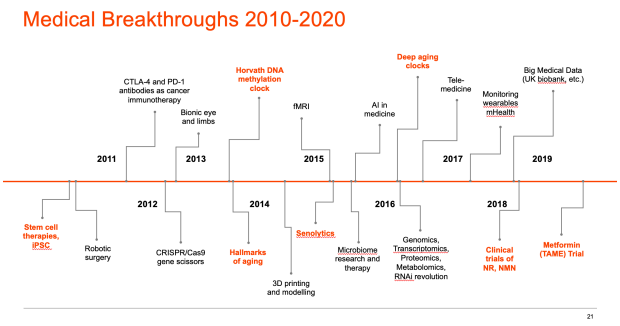
Anderson, L. A., Goodman, R. A., Holtzman, D., Posner, S. F., & Northridge, M. E. (2012). Aging in the United States: opportunities and challenges for public health. American journal of public health, 102(3), 393–395. https://doi.org/10.2105/AJPH.2011.300617

Cutler, R. G., & Mattson, M. P. (2006). Introduction: The adversities of aging. Ageing research reviews, 5(3), 221-238.*

Lutz W, Sanderson W, Scherbov S. The coming acceleration of global population ageing. Nature. 2008 Feb 7;451(7179): 716-9. doi: 10.1038/nature06516. Epub 2008 Jan 20. PMID: 18204438.*

From biogerontology to clinic: geroscience and longevity medicine





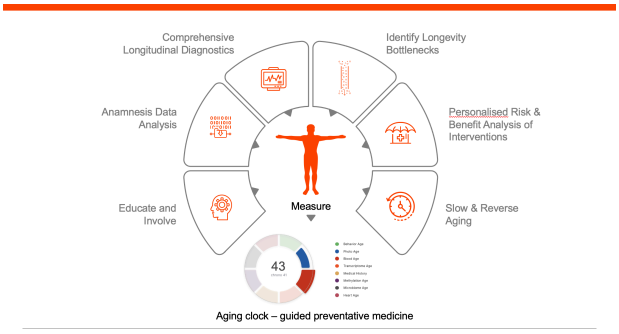
As mentioned before, in order to delay the diseases of old age, it is necessary to develop interventions against their main cause — aging. Biogerontologists have been studying the mechanisms of aging for over 100 years. Despite the fact that its main successes were achieved in laboratories on model animals, in recent years, more and more encouraging results with high potential for humans have been obtained.

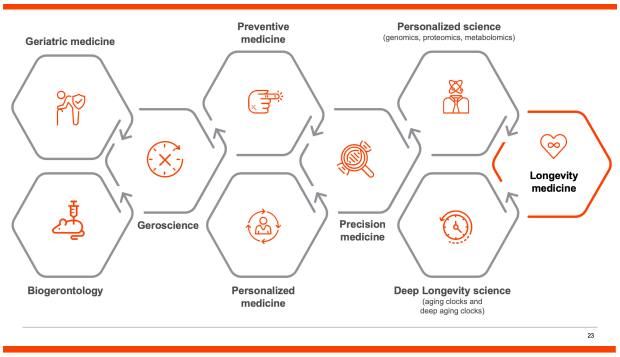
Achievements of the fundamental research of aging and longevity are being accelerated. Over the past 10 years they have been integrated with the advances in medical technology to diagnose and treat aging-related diseases. The biomedical aspects of aging research can be divided into three interrelated, yet distinct study fields. It is essential to understand this classification before we proceed any further:

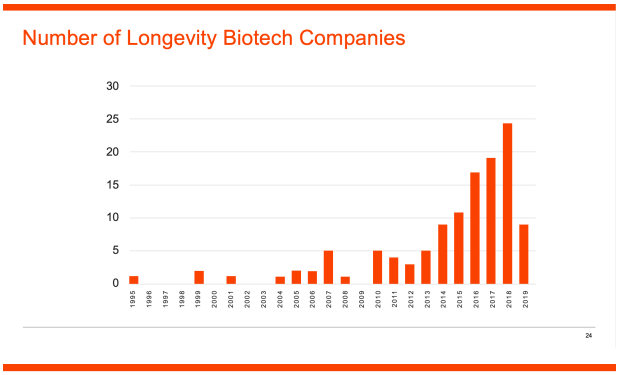
Geriatry or geriatric medicine —diagnostics and therapeutics in the elderly, including palliative care. According to the apt expression of David Sinclair, it is engaged in the treatment of age-related diseases with a 30-year long delay.

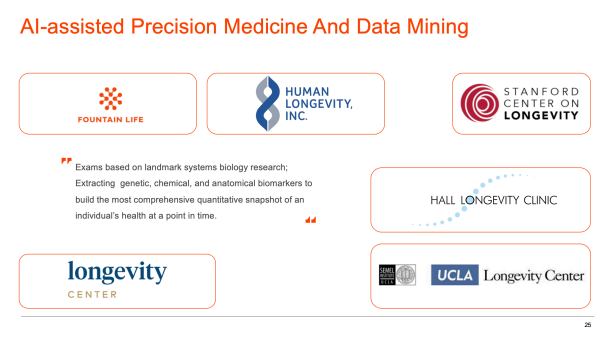
Biogerontology — mainly focused on experimental applications that can slow down or reverse aging (geroprotectors, aging clocks, gene and cell therapies, artificial organs). Biogerontologists consider aging an independent phenomenon and not a blanket term for multiple diseases. Most biogerontology studies are carried out in laboratory conditions and model animals.

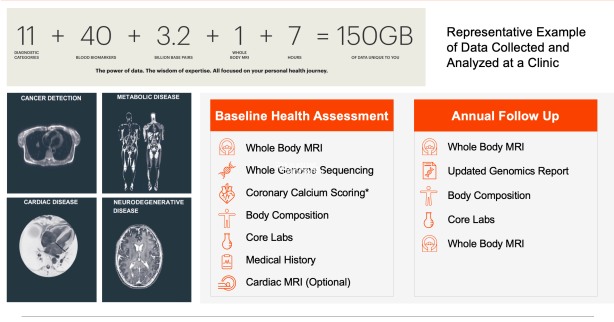
Geroscience — scientific domain that explores the genetic, molecular, and cellular mechanisms which render aging a major driver of diseases and chronic conditions. Thanks to this approach, several clinical studies of geroprotectors (metformin, NMN, senolytics, rapalogs) in older people have been launched. The achievements in geroscience are expected to turn preventive, personalized medicine from a concept into viable











solutions. From a geroscientific point of view, the health of each patient is considered as a complex scientific problem, which needs to be solved by the means of -omics technologies and targeted intervention.

Longevity Medicine is the final destination of geroscience. Longevity Medicine should be considered personalized precision theragnostics, in which a large number of aging clocks are monitored and targeted, systematic interventions are offered for the prevention and treatment of chronic diseases.

It is gratifying to note that the number of companies and start-ups aimed at applying the principles of geroscience to medical practice is growing every day. Recently, some clinics have emerged that focus on the use of big data and artificial intelligence for their analysis to enable the personalized preservation of the patient's health.

Recommended literature for a more in-depth study:

Web-source:

https://www.nia.nih.gov/research/dab/geroscience-intersection-basic-aging-biology-chronic-disease-and-health

Sierra F. The Emergence of Geroscience as an Interdisciplinary Approach to the Enhancement of Health Span and Life Span. Cold Spring Harb Perspect Med. 2016;6(4):a025163. Published 2016 Apr 1. doi:10.1101/cshperspect.a025163

Kaeberlein M. Translational geroscience: A new paradigm for 21st century medicine [Internet]. Transl. Med. Aging 2017;1:1–4.

Kennedy BK, Berger SL, Brunet A, Campisi J, Cuervo AM, Epel ES, Franceschi C, Lithgow GJ, Morimoto RI, Pessin JE, Rando TA, Richardson A, Schadt EE, Wyss-Coray T, Sierra F. Geroscience: linking aging to chronic disease. Cell. 2014 Nov 6;159(4):709-13. doi: 10.1016/j.cell.2014.10.039. PMID: 25417146; PMCID: PMC4852871.

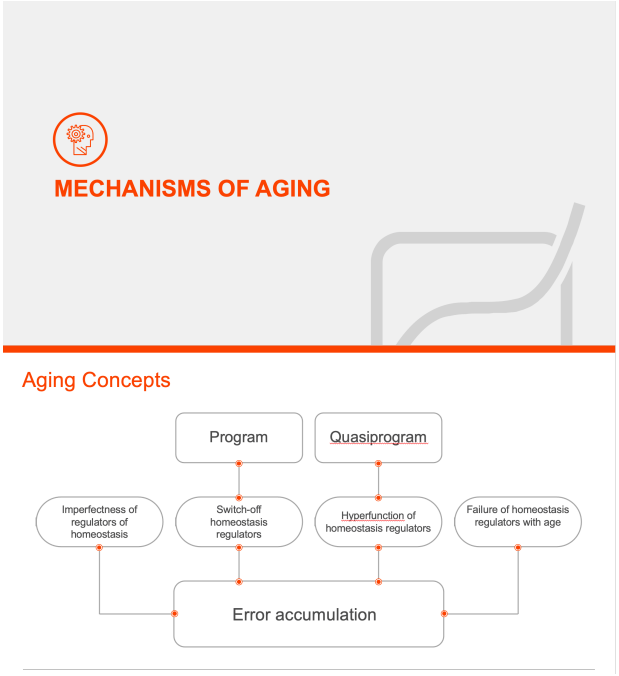
What is aging?

Aging per se can be described as the accumulation of extra- and intracellular damage in the form of molecular aggregates, mitochondrial dysfunction, chronic inflammation , fibrosis and decreased regeneration. It can also be defined as a preclinical or presymptomatic stage of age-related diseases, such as: myocardial infarction, stroke, sarcopenia, type 2 diabetes mellitus, cataracts, cancer, arthritis, Alzheimer's disease, Parkinson's disease… Aging is also the cause of homeostasis disruption, which causes an increase in morbidity, mortality and general frailty risk.

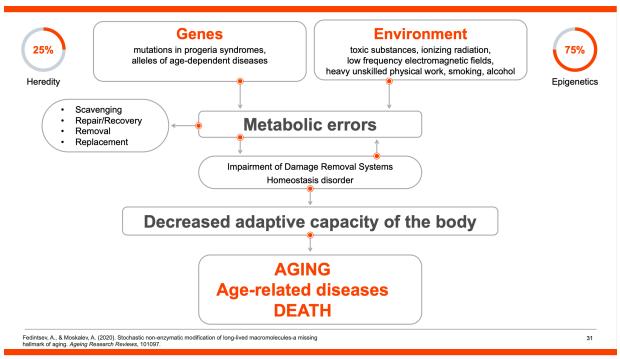
Recommended literature for a more in-depth study:

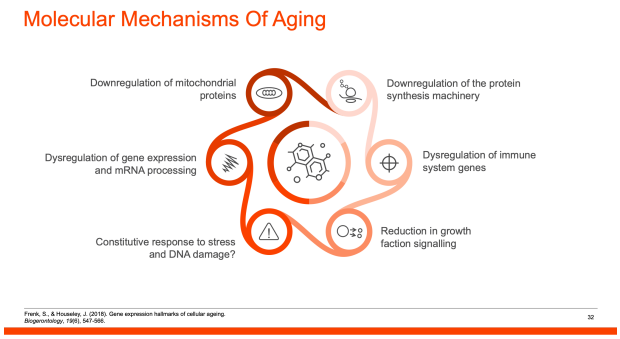
Rose, M. R., Flatt, T., Graves, J. L., Greer, L. F., Martinez, D. E., Matos, M., Mueller, L. D., Shmookler Reis, R. J., & Shahrestani, P. (2012). What is Aging?. *Frontiers in genetics*, *3*, 134. https://doi.org/10.3389/fgene.2012.00134

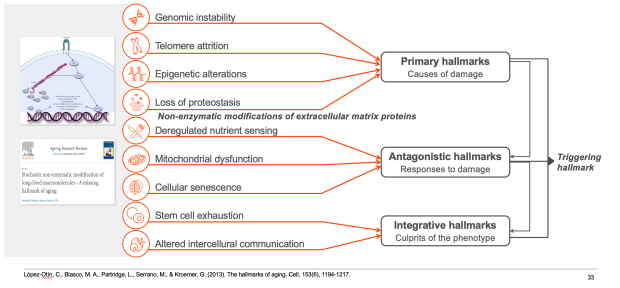
Mechanisms of aging

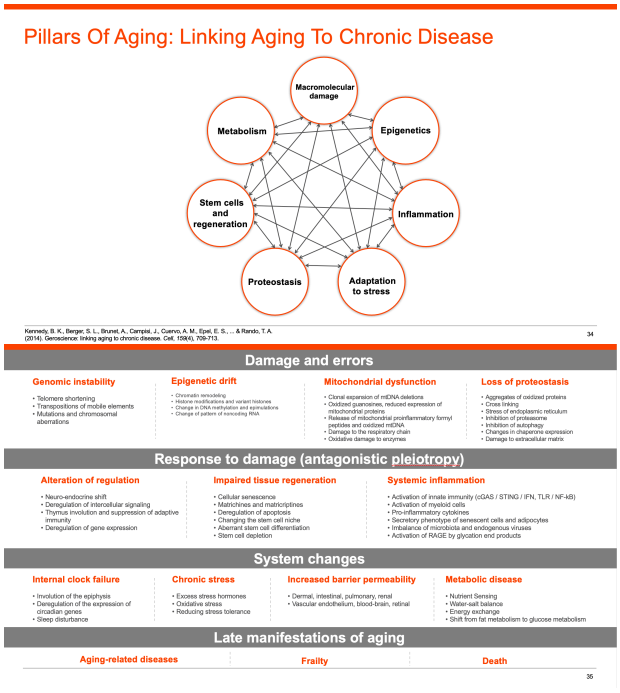


According to modern concepts, aging is the accumulation of errors at different levels of organization of a living system: molecular, cellular, tissue, organ-specific and systemic. However, views on the causes of this accumulation can vary. Some authors (*Gladyshev, Golubev*) believe that the main reason for the accumulation of errors is the inability of the cell's reparative systems to eliminate certain types of damage. Proponents of programmed aging (*Skulachev, Mittendorf*) postulate the existence of evolutionary deterministic mechanisms that are induced at certain stages of ontogenesis for the elimination of an individual to free up space and resources for the next generation. It should be noted that any genes, hormones, or body structures that have been evolutionarily established to start aging have not been identified in humans. According to another point of view, aging is a quasi-program that is a side effect of hyperactivation of compensatory mechanisms in response to the gradual accumulation of damage and errors. Finally, the more generally accepted point of view is that the exponential rate of error accumulation is explained by the gradual failure









of the repair and maintenance systems.

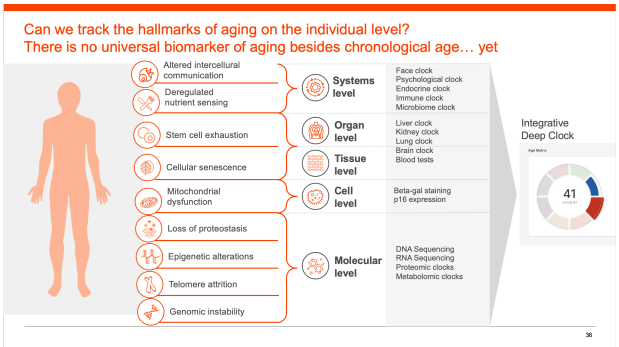
Metabolic errors accumulate rate varies for different individuals. The rate is partly (10-25%) determined by hereditary predisposition. Some examples of the hereditary component of aging are: mutations in Werner and Hutchinson-Gilford progeria syndromes, cancer-, diabetes-, atherosclerosis-, and dementia-associated genes. However, to a much greater extent, metabolic errors are associated with the influence of factors in the internal and external environment: toxins, ionizing radiation, smoking, alcohol, heavy physical exertion, reactive oxygen and nitrogen species, activation of aging-associated signaling pathways by particular metabolites (methionine, BCAA, oxysterols, AGEs). It is worth noting that epigenetics is involved in this case, since all these factors affect the activity of genes. In a healthy young body, the instances of metabolic errors get scavenged, repaired, removed, or replaced. However, breakdowns gradually accumulate with age in these recovery systems themselves, which leads to impaired homeostasis maintenance and adaptive capabilities.

Hallmarks of aging are numerous and listing them all requires some kind of classification. All the components of aging, sucha as the dysregulation of gene expression or DNA mutations, can be divided into primary damage, response to damage and systemic phenomena:

- **Primary damage**: genomic instability, loss of proteostasis, epigenetic changes, respiratory damage, non-enzymatic modifications and fragmentation of the extracellular matrix;
- **Inadequate response to damage**: deregulation of nutrient sensing, mitochondrial dysfunction, cellular aging;
- **Systemic**: depletion of the stem cell pool and impaired intercellular communication.

Each of these categories can be expanded into even more specific subjects. For example, the primary damage manifests as:

- **Genomic instability**: shortening of telomeres, transposition of mobile genetic elements, mutations and chromosomal aberrations;
- **Epigenetic changes**: chromatin remodeling, changes in DNA methylation and epimutation, histone modifications and changes in the proportion of variant histones, altered patterns of noncoding RNAs;



· **Loss of proteostasis**: aggregates of carbonylated, cross-linking of long-lived intra- and extracellular proteins, endoplasmic reticulum stress, proteasome and autophagy inhibition, changes in chaperone expression, fragmentation of the extracellular matrix;

· **Respiratory damage**: clonal expansion of mtDNA with deletions, accumulation of oxidized guanosine in mtDNA, decreased expression of mitochondrial genes, release of inflammatory formyl peptides and oxidized circular DNA from mitochondria, damage to the respiratory chain and mitochondrial enzymes, decreased LON protease activity.

While these damaging processes are harmful on their own, a hypertrophied response to them is no less dangerous. As aging progresses, stress response systems tend to become more erroneous and cause:

· **Dysregulation of physiological functions**: neuro-endocrine shifts, deregulation of intercellular signaling, involution of the thymus and suppression of adaptive immunity with simultaneous hyperfunction of innate immunity (inflammation), epigenetic deregulation of gene expression;

· **Deterioration of tissue regeneration**: permanent cell cycle arrest, cytotoxic and inhibitory effects on the proliferation of matricriptins arising from fragmentation of the extracellular matrix, deregulation of apoptosis, changes in stem cell niches (leading to a predominance of differentiation over stem cell renewal), ablation cells and depletion of their number.

· **Systemic inflammation**: activation of cGAS / STING / IFN, AGEs / RAGEs and TLR / NF-kB signaling pathways, pro-inflammatory myeloid cells, the release of inflammatory cytokines by these and senescent cells, gut microflora imbalance.

Taken together, primary damage and hyperreactive stress response produce systemic changes, including:

· Deregulation of the internal clock;

· Chronic stress;

· Increased permeability of tissue barriers;

· Metabolic syndrome.

Understanding these mechanisms allows developing aging biomarkers that can be used to monitor age-dependent changes in individuals on a molecular level. Tracking aging in humans is

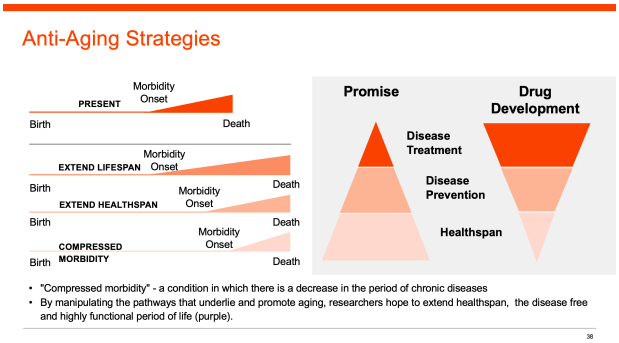
achieved with aging clocks, which in their turn help in creating new hypotheses and can be used to verify the efficacy of anti-aging therapies.

Recommended literature for a more in-depth study:

Fedintsev, A., & Moskalev, A. (2020). Stochastic non-enzymatic modification of long-lived macromolecules-a missing hallmark of aging. *Ageing Research Reviews*, 101097.

Frenk, S., & Houseley, J. (2018). Gene expression hallmarks of cellular ageing. *Biogerontology*, *19*(6), 547-566.

Therapies and interventions in longevity medicine



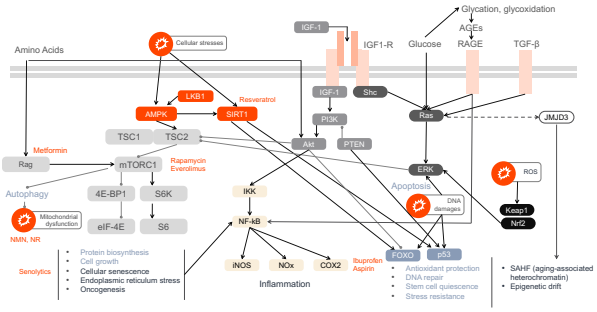
Conventional medicine is mostly focused on prolonging life, including the period of morbidity and frailty. Healthy lifestyle, early diagnostics and active prevention, on the other hand, help shift the period of chronic morbidity to an older age. This approach is focused on extending the healthy, productive part of life first and foremost. Therapeutics in longevity medicine aim to fight aging directly and compress the period of frailty.

Due to its mostly preventive approach, longevity medicine places extra emphasis on managing individual environment, medical checkups, forming healthy behaviors and psychological wellness. Let us look into what the most common longevity intervention achieve.

The most prominent longevity intervention is caloric restriction — reduction of calorie intake to a level that does not compromise overall health. Since this pattern is not practical for most patients, more convenient alternatives emerged: fasting mimicking diet, intermittent fasting, keto diet and 16:8 diet.

Other than dietary optimization, regular exercise is frequently prescribed. In epidemiological studies and meta-analyses, periodic exercise (aerobic and resistance training) has been shown to significantly reduce the risks of cancer, depression, cardiovascular disease, type 2 diabetes, sarcopenia, and osteoporosis. Exercise reduces levels of inflammation, visceral fat,

Nutrition and geroprotectors can affect basic mechanisms of aging



Nutritional Longevity Interventions

Caloric restriction (CR), reduction of calorie intake to a level that does not compromise overall health, has been considered as being one of the most promising dietary interventions to extend lifespan in humans.

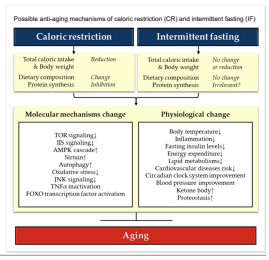
But - not practical!

Therefore:
Recently, fasting-related interventions such as intermittent fasting (IF) and time-restricted feeding (TRF) have emerged as alternatives of CR.

Or:

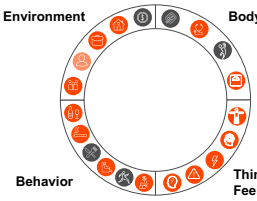
Individualized, evidence-based alimentary plans:

Dietary intake of total, animal, and plant proteins and risk of all cause, cardiovascular, and cancer mortality: systematic review and dose-response meta-analysis of prospective cohort studies



Personal Healthy Lifestyle Profile

Visualization of the "profile wheel" resulting from an extensive 360° diagnosis. The profile wheel is constructed of four quadrants: environment, body, behavior and thinking and feeling. The quadrants are further split up in sub-domains, including glucose metabolism, body composition (body), medication use (behavior) and loneliness (environment). The colors represent the traffic light model, with green representing a healthy score for a sub-domain, orange an in-between state and red an unhealthy score



Physical Training

Tumor diseases
Depression
Vascular stiffness
Ischemic changes in the myocardium
Visceral fat, type 2 diabetes risk
Metabolic health
Skin condition

arterial stiffness, and improves venous return, microcirculation, and blood supply to the myocardium and brain. Regular exercise improves metabolic health, the condition of many internal organs and skin.

Rest is just as important as healthy physical stress. During deep sleep, intensive cerebral regeneration takes place, which is crucial for maintaining intact cognitive functions and reducing the risks of neurodegeneration. The duration of deep sleep decreases with age and extra attention is required to normalize it.
Key sleep quality recommendations include:

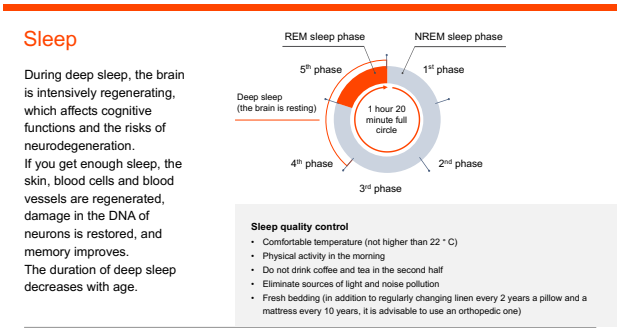
- Comfortable temperature (<22°C);
- Physical activity in the morning;
- Avoiding coffee and tea intake in the second half of the day;
- Elimination of light and noise pollution;
- Fresh bedding in addition to regular changing of linen every 2 years, pillow and mattress every 10 years;
- Using orthopedic mattresses.

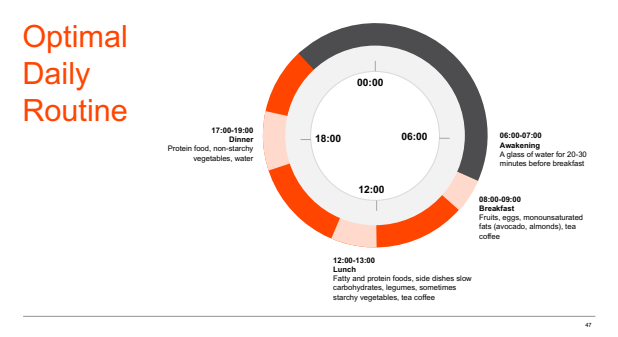
Next level of anti-aging interventions include geroprotectors. Geroprotectors are substances or interventions that aim to reduce the aging rate and prevent the onset of the aging-related disease. Thus, they should be administered before such diseases emerge. In experiments with model animals, geroprotective properties have been determined for several hundred compounds. At the same time, a potential human geroprotector must meet several criteria to be adopted for medical practice:

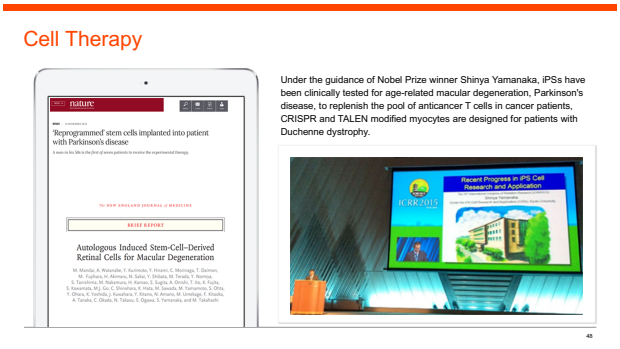
- life extension in wild-type animal models;
- improvement of aging biomarkers in humans;
- low toxicity;
- minimal side effects;
- quality of life improvement.

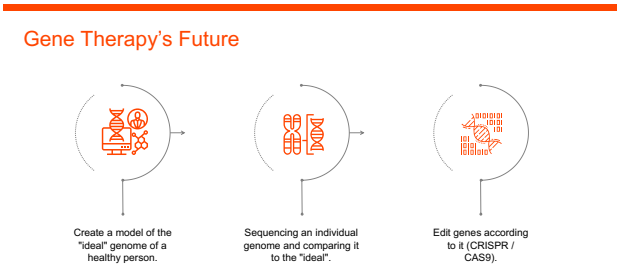
Geroprotectors target the key players in aging and longevity. The most promising therapies act via:

- Controlled activation of longevity genes (FOXO, AMPK, NRF2, Klotho and others);
- Inhibition of mTOR, S6K, TGF-β, AT1;
- Recovery of NAD+ levels;
- Elimination of senescent cells;
- Maintaining the acidity of lysosomes;
- Suppression of chronic inflammation;
- Elimination of protein cross-links;
- Telomere elongation;









· Elimination of aneuploidy and chromosomal instability;
· Suppression of retrotranspositions;
· Recovery of heterochromatin.

There are two online databases of potential geroprotectors. The first one is geroprotectors.org. It includes 259 compounds that extend lifespan in at least one of 13 model organisms from yeast to human. DrugAge is the other database and it contains more than 400 compounds tested for extending lifespan. Some of these compounds are FDA approved, and this gives hope for an increase in the number of clinical trials for the multimorbid conditions associated with aging.
Currently, several groups of compounds are known to have effect on one or more aging processes:
· Rapamycin;
· Senolytics;
· Metformin;
· Acarbose;
· Spermidine;
· NAD + enhancers;
· NSAIDs;
· Lithium;
· Reverse transcriptase inhibitors;
· Systemic circulating factors;
· Glucosamine;
· Glycine;
· 17α–oestradiol.
Since different geroprotectors affect different targets and mechanisms of aging, using their combinations either as cocktails or sequential mini-cycles is a promising perspective.

Other promising compounds that target various aging mechanism and being actively studied for their possible anti-aging effects include:
· RAGE antagonists;
· Anti-amyloid compounds;
· Extracellular matrix turnover stimulators;
· PPARγ / PGC-1α activators;
· NAD+ precursors;
· Prebiotics, metabiotics and enterosorbents;
· Antifibrotic agents;
· Neurotrophic factors;
· Anti-sarcopenia agents ;
· Factors preventing impairment of intestinal, endothelial, blood-brain, kidney, and skin barrier

function.
Some of the mentioned geroprotectors have progressed from the academic research stage and are now being tested in clinical trials: dPUFA, metformin, everolimus, urolithin. Adopting geroprotectors into conventional medicine, however, is difficult, since there are no universally accepted biomarker panels to measure their efficacy. The field of biohorology (measuring the aging rate via aging clocks) is mostly contained within the academia and alternative approaches are being actively debated.

And although some anti-aging therapies are already on the way, the search for more potent geroprotectors and combinations thereof is never ending. Modern discoveries in the field of longevity genetics have made it possible to identify dozens of potential targets for new interventions (AMPK, SIRT1, mTOR, NF-kB, IGF1-R, p53, FOXO, etc.). Many of these targets can also be introduced or regulated by food nutrients.

Strictly speaking, all the geroprotectors we discussed are only gerosuppressors — they may slow down, but not reverse aging. In its turn, cell therapy has the potential to provide true rejuvenation. Induced pluripotent stem cell (iPSCs) technology pioneered by Shinya Yamanaka has been in clinical trials since 2008. It has been tested for treating such age-related diseases as macular degeneration, Alzheimer's, and cancer. Dozens of clinical trials are still ongoing.
Gene therapy is the next step for in anti-aging therapeutics. For example, CRISPR and TALEN gene editing methods can be used to modify myocytes in Duchenne dystrophy patients. In future a concept of a "healthy genome" may emerge and on-demand allele editing to approach it might become a regular occurrence.

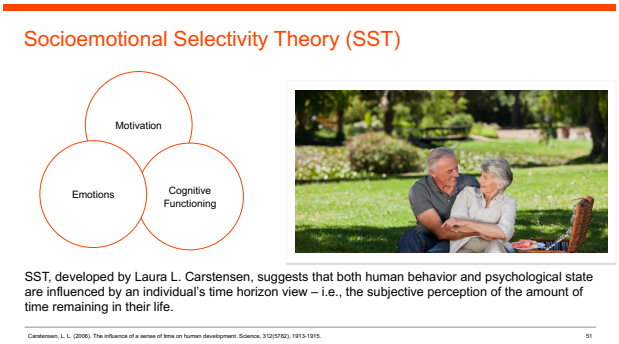
Recommended literature for a more in-depth study:

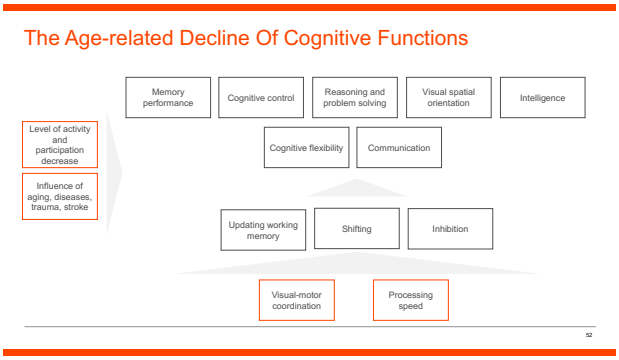
Naghshi, S., Sadeghi, O., Willett, W. C., & Esmaillzadeh, A. (2020). Dietary intake of total, animal, and plant proteins and risk of all cause, cardiovascular, and cancer mortality: systematic review and dose-response meta-analysis of prospective cohort studies. *bmj*, *370*.

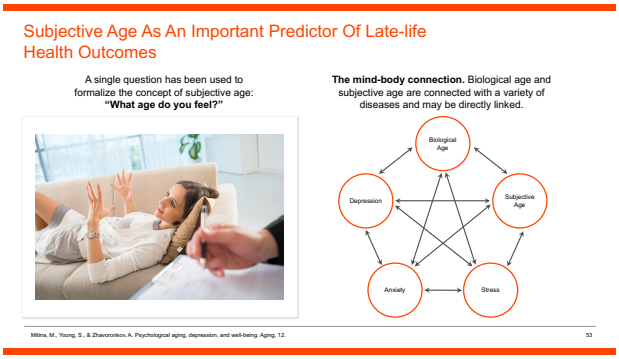
Kennedy, B. K., Berger, S. L., Brunet, A., Campisi, J., Cuervo, A. M., Epel, E. S., ... & Rando, T. A. (2014). Geroscience: linking aging to chronic disease. *Cell*, *159*(4), 709-713.
Web resource:

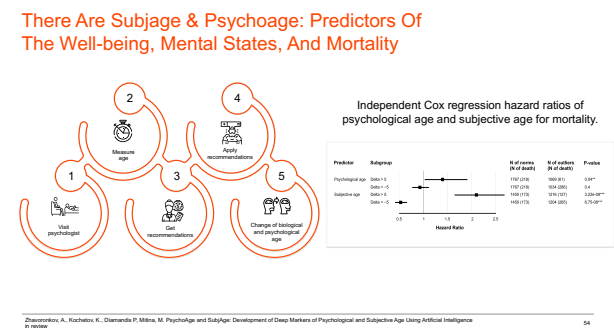
https://bioinformant.com/ips-cell-clinical-trials/

Psychology of aging









Psychology of aging is a crucial component of longevity medicine. Life events have implications on human psychology, behavior, values and principles.

The socioemotional selectivity theory by Laura L. Carstensen

In the absence of medical interventions human lifespan is shortened. After the industrial revolution humans had to adjust to the gradual increase of the elderly population both as a society and at an individual level. Rising life expectancy has led to substantial variability in the perception of age. Individuals may perceive themselves and others as substantially younger or older than their chronological age — this produces the subjective age concept.

The perception of subjective age may have profound effects on behavior and well-being, and is connected to an individual's lifespan. The socioemotional selectivity theory developed by Laura L. Carstensen at Stanford University, maintains that "the perception of time plays a fundamental role in the selection and pursuit of social goals". An extended perception of time enables the long-term outlook and may lead to more knowledge-based motivations and choices. Conversely, when the perception of time is limited to short term, a person may choose more emotion-based options. This theory and the associated studies have highlighted the importance of the psychology of aging as a field of research and laid the foundation for studies of psychological and psychophysiological aging markers.

Terms:

Emotion is a complex reaction pattern, involving experiential, behavioral and physiological elements".

Motivation is the impetus that gives purpose or direction to behavior and operates in humans at a

conscious or unconscious level. Motives are frequently divided into (a) physiological, primary, or organic motives, such as hunger, thirst, and need for sleep; and (b) personal, social, or secondary motives, such as affiliation, competition, and individual interests and goals. An important distinction must also be drawn between internal motivating forces and external factors, such as rewards or punishments that can encourage or discourage certain behaviors.

Cognitive functioning is the performance of the mental processes of perception, learning, memory, understanding, awareness, reasoning, judgment, intuition, and language. **[**In normal aging, a wide range of cognitive functions are subject to age-related decline]

(American Psychological Association)

Subjective age

When it comes to psychological health, a person's subjective psychological constructs may be more valuable than previously thought. Various studies have examined a number of subjective psychological concepts to understand psychological aging. These concepts include subjective age, age identity, the aging self, attitudes toward one's own aging, self-perceptions of aging, and satisfaction with aging.

Historically, a single question has been used to formalize the concept of subjective age: "What age do you feel?" Age identity is defined as the difference between subjective age and chronological age ("Are you younger/older than your real age?"). An alternative approach for determining subjective age involves asking participants whether they feel psychologically and physically younger, older, or the same as their chronological age. Further variations on this approach include asking participants to match themselves with a specific age group, such as middle-aged or older, or with a cognitive age (i.e., feel-age, look-age, do-age, and interest-age).

These classifications require greater implementation in longitudinal studies. In a recent study by Veenstra et al. an analysis of longitudinal national survey data showed that a desire to be younger than one's chronological age

may be associated with lower life satisfaction and lower physical activity in the second half of a person's life. Thus, enhanced life enjoyment is correlated with higher age satisfaction. This data raises the question of what an individual's ideal age is, which can be interrogated by the following prompt: "If you could choose your age, what age would you like to be?" Another measure, which could be applied in clinical practice are questions about visually perceived age. This approach defines the age of participants by the perception of digital photos or physical appearance. The Longitudinal Study of Aging Danish Twins demonstrated that perceived age estimated from photographs could be used as a predictor of mortality in the volunteers.

Recommended literature for a more in-depth study:

Carstensen LL, Isaacowitz DM, Charles ST. Taking time seriously. A theory of socioemotional selectivity. Am Psychol. 1999; 54:165–81. https://doi.org/10.1037//0003-066x.54.3.165

Mitina M, Young S, Zhavoronkov A. Psychological aging, depression, and well-being. Aging (Albany NY). 2020; 12:18765-18777. https://doi.org/10.18632/aging.103880

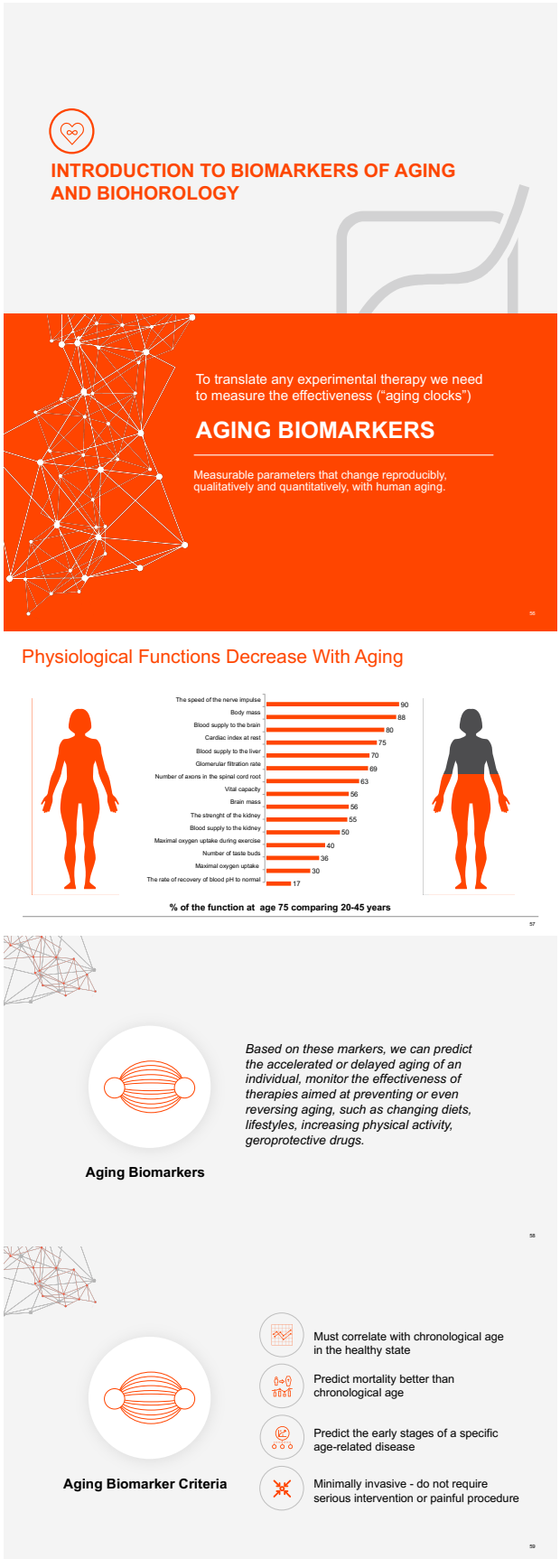
Westerhof GJ, Wurm S. Longitudinal research on subjective aging, health, and longevity: Current evidence and new directions for research. Annual Review of Gerontology and Geriatrics. 2015; 35:145–65. https://doi.org/10.1891/0198-8794.35.145

Diehl M, Wahl HW, Barrett AE, Brothers AF, Miche M, Montepare JM, Westerhof GJ, Wurm S. Awareness of aging: theoretical considerations on an emerging concept. Dev Rev. 2014; 34:93–113. https://doi.org/10.1016/j.dr.2014.01.001

Barak B, Stern B. Subjective age correlates: a research note. Gerontologist. 1986; 26:571–78. https://doi.org/10.1093/geront/26.5.571

Uotinen V, Rantanen T, Suutama T. Perceived age as a predictor of old age mortality: a 13-year prospective study. Age Ageing. 2005; 34:368–72. https://doi.org/10.1093/ageing/afi091

Veenstra M, Daatland SO, Aartsen M. The role of subjective age in sustaining wellbeing and health in the second half of life. Ageing Soc. 2020; 1–21. https://doi.org/10.1017/S0144686X2000032X



Introduction to biomarkers of aging and biohorology

Biohorology is the science of measuring the passage of time in living systems. Chronological age is the number of years a person has been alive, while biological age refers to how old a person seems functionally. Both are measured with technologies called “aging clocks“.

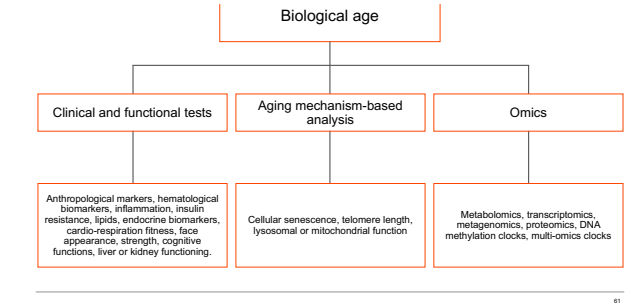
There is a variety of aging clocks based on such biomarkers of aging as DNAm, gene expression and metabolic profiles. DNAm clocks are the most popular so far, but they have a number of frequently overlooked technical drawbacks. Deep learning methods are now being used to develop aging clocks using data types previously deemed too complicated and to extend aging clocks’ functionality beyond age prediction.

In order to target aging, it is necessary to reproducibly measure it both quantitatively and qualitatively. Aging biomarkers are the parameters that can be used for this, since they correlate well with human functional decline. Certain age-related changes in the body may serve the purpose of monitoring the rate of aging and the effectiveness of aging interventions.

Based on these markers, we can evaluate if a person aging rate is accelerated or delayed. This enables the scientists to establish the effectiveness of anti-aging therapies, such as dietary, pharmacological or behavioral interventions.

To qualify for an aging biomarker a biological parameter needs to follow these criteria:

- High correlation with chronological age in healthy individuals;
- Can be used to predict mortality better than chronological age;
- Indicative of the risk of onset for age-related diseases;
- Minimally invasive sample collection procedures;
- Sensitive to early signs of aging, as opposed to mortality and frailty;



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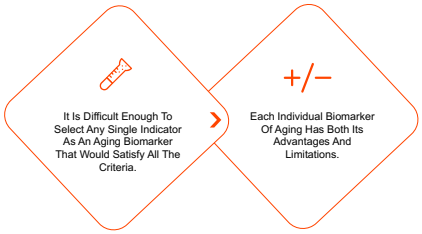
The Combination Of Biomarkers



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- Low analytic variability, robust and reproducible results.

Recommended literature for a more in-depth study:

Putin, E., Mamoshina, P., Aliper, A., Korzinkin, M., Moskalev, A., Kolosov, A., ... & Zhavoronkov, A. (2016). Deep biomarkers of human aging: application of deep neural networks to biomarker development. *Aging (Albany NY)*, *8*(5), 1021.

Belsky, D. W., Moffitt, T. E., Cohen, A. A., Corcoran, D. L., Levine, M. E., Prinz, J. A., ... & Caspi, A. (2018). Eleven telomere, epigenetic clock, and biomarker-composite quantifications of biological aging: do they measure the same thing?. *American Journal of Epidemiology*, *187*(6), 1220-1230.

Mamoshina, P., Kochetov, K., Cortese, F., Kovalchuk, A., Aliper, A., Putin, E., ... & Zhavoronkov, A. (2019). Blood biochemistry analysis to detect smoking status and quantify accelerated aging in smokers. *Scientific reports*, *9*(1), 1-10.

Galkin, F., Aliper, A., Putin, E., Kuznetsov, I., Gladyshev, V. N., & Zhavoronkov, A. (2018). Human microbiome aging clocks based on deep learning and tandem of permutation feature importance and accumulated local effects. *BioRxiv*, 507780.