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Research Article

Biological Age: From Philosophy to Science an Integrative Systematic Review

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Summary

The objective was to analyze the scientific production on biological age and available resources to estimate it. This is an integrative systematic review carried out in PUBMED/Medline, LILACS, SciELO and Google Scholar databases, using the descriptors indexed in Health Science Descriptors (DeCS) and Medical Subject Headings (MeSH): Biological Age, Longevity and Biological Markers. Inclusion criteria: articles with full text, published in Portuguese and English, qualitative or quantitative, with definition of biological age and/or its measurement tools (biological markers). Publications that did not address the established theme, congress abstracts, annals, editorials, comments and opinions were excluded.

A total of 31 articles published between the years 1996 and 2022 were obtained. No single biomarker seems to have a safe correlation with biological age; therefore, it is fundamental to look for reliable biomarkers in the identification of individuals vulnerable to loss of functionality resulting from the age. Research includes immunological and inflammatory markers, DNA methylation, telomere length, among others, but studies involving multiple pathways interaction, practicality and low cost is the target of many of this research. Deep learning, or Deep Learning, is rapidly becoming a tool present in all areas of science and will undoubtedly be essential for accurate estimates of biological age and, consequently, for developing interventions against most chronic diseases and perhaps the very aging process.

Keywords: Biological Age; Longevity; Biological Markers

Introduction

The phenomenon of world population aging has driven the search for a better quality of life for this segment, through the promotion of healthy and active aging [1]. Estimating the health of the elderly person based on their chronological age is inadequate, as senescence does not occur uniformly among people and, even in the same individual, organs and tissues have an individualized rhythm [2]. Thus, one retrospective time marker–chronological age–is insufficient to translate organic aging [3]. The possibility of reaching advanced chronological ages with good physical and cognitive performance has been widespread in different population spheres. Currently, efforts are being made to delay the aging of organisms and monitoring intrinsic capacity can be done by measuring biological age [1].

Although static chronological parameters are used by the World Health Organization (UN) and support public policies aimed at aging, Sergei Scherbov and Warren C. Sanderson [3] consider the chronological estimate outdated because it does not take into account the different intrinsic and extrinsic exposures. These

authors propose biological age as representative of contemporary elderly people, who remain healthy, strong and cognitively functional. Biological age appears in an opportune and innovative way, allowing the change of the stereotype of the elderly person and contributing positively to the socioeconomic context of those who reach the 7th decade of life who may be part of the economically active population (EAP) of a country [3,4].

Biological age is defined as the indication of the body's general state of health that establishes the degree of aging according to body functioning, associating it with genetic factors and factors extrinsic to the individual. In this sense, biological age is understood as a prospective age that proposes to analyze future repercussions on the individual's health and, according to Sanderson and Scherbov 2010, 2013. this age corresponds to a remaining life expectancy of 15 years [3].

It is difficult to conceive the exact date on which the gaze turned beyond numerical age and the term biological age was coined. Historically, in 1996, L. Hayflick broke paradigms when he dissociated the concept of time from the aging process. In his approach, aging is not just past events, but a consequence of biological manifestations over time [5]. When analyzing the disparities between aging, it is noticed that these extrapolate the clinically pre-established chronological intervals, as in the cases of cardiovascular diseases that are presented in the literature with clinical manifestations around the 6th and 7th decades of life, it is notorious that the beginning these vascular diseases and their mortality are epidemiologically variable among individuals [6].

Understanding and mapping the physiological processes that determine the wear and tear of organisms is one of the main challenges of gerontology today, in order to adopt increasingly individualized postures in the face of clinical manifestations [5]. The important reflections on the aging of the organism in the mid-1990s were faced with insufficient technology to measure biological age. This mismatch between advances in scientific thinking and technology lasted until 2002, a period in which defining biological age was considered by some authors entertainment and not science [7]. In the current scenario, with all the changes that have occurred at the beginning of the 21st century in the field of medicine and technology, and with the extension of longevity, the break with the chronological definition of aging gained space for discussion in the editorials of scientific journals with the discovery of biological markers of senescence [7]. Knowing the biological mechanisms that govern the aging process is important, as other physiological processes are already known and well defined, such as puberty and menopause. The current challenge has been to find the biological markers that can definitively establish the beginning of the human senescence process [8].

Parallel to childhood development milestones, it is possible to obtain aging milestones. The study of biomarkers that include changes in gene expression and concentrations of metabolites, epigenetics, telomere wear and deep learning are established in the identification of these milestones. Deep learning, one of the most sophisticated and current estimators of biological age, proposes, through samples of peripheral blood, physical activities and body shapes, to understand the health of individuals based on algorithms. This study seeks to generate repercussions in promoting the health of the elderly and contribute to advances in medical science mediated by artificial intelligence [9].

Methodology

The integrative systematic review method was adhered to as it meets targets such as reviewing theories or evidence and compiling knowledge about a specific topic, promoting recognition of gaps to be filled with new research. The following steps were observed: a) formulation of the leading question; b) definition of inclusion and exclusion criteria; c) delineation of descriptors, literature search and data collection; d) critical evaluation of included studies and discussion of results; e) publication of the knowledge obtained [10,11]. The selection of articles took place from November to December 2022, guided by the question: What is biological age and how to estimate it?

Only articles that met the following inclusion criteria were selected: published in Portuguese and English, qualitative or quantitative, with definition of biological age and/or its measurement tools (biological markers), published between 1996 and 2022, available in the following databases: National Library of Medicine (MEDLINE/PubMed), Latin American and Caribbean Health Sciences Literature (LILACS), Scientific Electronic Library Online (SciELO) and Google Scholar. Publications that did not address the established theme, congress abstracts, annals, editorials, comments were excluded.

To search for articles, the following descriptors indexed to Health Science Descriptors (DeCS) and Medical Subject Headings (MeSH) were used: Biological Age, Longevity and Biological Markers. As search strategies, the descriptors were combined using Boolean operators (AND and OR). All articles selected from the keywords had their abstracts read in full, and those that were not within the established criteria and/or were repeated in the different databases. were excluded. In the identification phase, 104 articles were found. Considering the criteria of pertinence and content consistency, as well as duplicates, 72 articles were excluded. In the end, 32 scientific articles were selected [Figure 1].

After full reading of the articles that met the inclusion criteria, the information was extracted, organized and summarized. This information was organized into 1) concepts of biological age; 2) biological markers for estimating biological age.

Results

The selected articles were summarized in the instrument for data collection. Initially, a descriptive analysis of the articles was carried out, covering the following items: title, reference, journal in which it was published, type of study and research location [Tables 1,2,3].

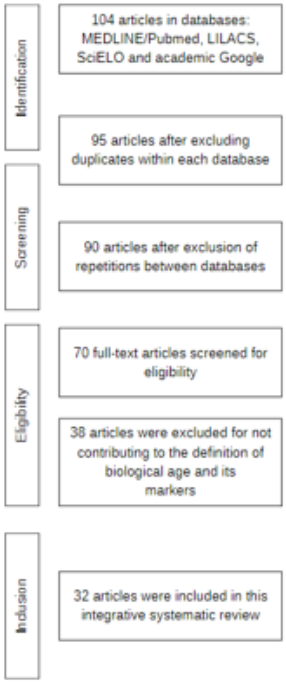

Figure 1: Flowchart of the research identification, screening and eligibility process.

Table 1: Description of the articles found according to the database.

Data base	Articles found	Pre-selected articles	Excluded Articles	Items included
Lilacs	7	3	0	3
Pubmed/Medline	59	50	32	18
Google acadêmico	38	21	12	10
Scielo	5	2	0	1
Total	109	77	44	32
Source: Authors, 2023				

Table 2: Articles that discuss the definition of biological age.

Article Title	Authors	Year	Definitions
How and why we age. Hayflick, L 1996 Aging is not the simple passage of time, but the biological manifestations that occur in the organism during the course of this temporal space". Chronological aging is just a convention, with no influence of time on the body.	Hayflick, L .	1996	Aging is not the simple passage of time, but the biological manifestations that occur in the organism during the course of this temporal space". Chronological aging is just a convention, with no influence of time on the body
Chronological Age: a mere referential question in the aging process	Lúcia Regina Severo Duarte	1999	Biological age, that is, physical and biological changes can serve to define aging. The rhythm of biological aging is very different depending on the individual, people of advanced age sometimes enjoy better health than others in full maturity or even young people. The notion of senectude cannot be centered on this biological facet;
Arterial stiffness as a marker of injury in the present and a predictor of risk in the future	Marcus Vinícius Bolívar Malachias	2004	The increase in arterial stiffness has been observed with aging, and may serve as a reference for the assessment of vascular biological age.

Aging today: chronological, biological, psychological and social aspects	Rodolfo Herberto SCHNEIDER Tatiana Quarti IRIGARAY	2006	Biological age is defined by body and mental changes that occur throughout the development process and characterize the human aging process, which can be understood as a process that begins before the individual's birth and extends throughout human existence.
Skeletal Maturation And Growth In Children And Adolescents	Dalmo Roberto Lopes Machado, Valdir J. Barbanti	2007	Biological age is understood as the age of an individual defined by maturation processes and exogenous influences. Thus, it is not uncommon to find different biological ages between individuals of the same chronological age. For its determination, indicators of skeletal, sexual or somatic maturation can be used.
The Perception Of The Elderly In Relation To Their Health	Marcella Villela Carvalho	2010	Biological age is defined by the changes that go through a person's body and mind, and, in the aging phase, the changes and losses that occur are shown.
Subjective Age And Its Relationships With Successful Aging	Samila Sathler Tavares Batistoni, Carina Sayuri Namba	2010	Biological age is conceived as an indicator of the time left for an individual to live, at a given moment in his life. Biological aging is the process that presides over or determines the potential of each individual to remain alive, which decreases over the years.
Hematological aspects of aging	Andrade, Rita , Costa, Elísio , Santos-Silva, Alice	2012	The chronological age of an individual can be different from the biological age. Certain biological variables, such as skin elasticity and arterial function (vascular aging), correlate linearly with chronological age, while other biological markers, such as lung capacity, hearing and cognitive function, as well as visual acuity, are not necessarily associated with chronological age. Exposure to risk factors and genetic predisposition influence biological age, allowing the distinction between biological and chronological age.
Integration of 'omics' data in aging research: from biomarkers to systems biology	Jonas Zierer, Cristina Menni, Gabi Kastenmüller, Tim D. Spector	2015	Biological age is a broader concept that takes into account individual physical and mental health, thus capturing individual differences in the aging process.
Characterization Of Telomeres As Molecular Biomarkers: Implications On The Establishment Of Biological Age	Telma Filipa Azevedo Resende	2015	Biological age is defined as a set of age-dependent variables, called biomarkers, which are quantified using statistical algorithms.
Aging: progressive decline in fitness due to the rising deleterious adjusted by genetic, environmental, and stochastic processes	Vadim N. Gladyshev	2016	Living is associated with a myriad of deleterious, random and deterministic processes, which are caused by imperfection, exhibit cumulative properties and represent the indirect effects of biological functions at all levels, from simple molecules to systems. From this derives the deleterious, which encompasses age-related deleterious cumulative changes and represents biological age.
New Approaches to the Conceptualization and Measurement of Age and Aging	Sergei Scherbov, Warren C Sanderson	2016	Chronological age is retrospective age and measures how many years a person has lived. Everyone of the same age lived the same number of years. In contrast, prospective age is about the future. It talks about the years of life to be lived.
Use of different methods for determining bone age in young people	Vanessa Carla Monteiro PINTO* Francisco Emílio Simplício de SOUZA* Thaisys Blanc dos Santos SIMÕES* Arnaldo Luis MORTATTI* Paulo Moreira Silva DANTAS* Breno Guilherme de Araújo Tinôco CABRAL*	2017	maturation is seen as a continuous and dynamic biological process, which begins at conception and ends at death. It is punctuated by visible changes in height, body composition and secondary sexual characteristics, which culminate in the transition from the pre-reproductive to the reproductive phase of the human life cycle. Skeletal maturation is widely recognized as the single best indicator of maturity status, and is considered to be a true record of biological age.

Biological Age is a predictor of mortality in Ischemic Stroke	Carolina Soriano-Tárraga, Eva Giralt-Steinhauer, Marina Mola-Caminal, Angel Ois, Ana Rodríguez-Campello, Elisa Cuadrado-Godia, Israel Fernández-Cadenas, Natalia Cullell, Jaume Roquer & Jordi Jiménez-Cond	2018	Biological age can be considered and used as a predictor of mortality in patients with ischemic stroke.
The concepts of old age and aging over time: contradiction or adaptation?	Cassia Figueiredo Rossi Dardengo and Simone Caldas Tavares Mafra	2018	Biological age is defined by bodily and mental changes that occur throughout the development process and characterize the human aging process.
Estimating Biological Age in the Singapore Longitudinal Aging Study	Xin Zhong, PhD, Yanxia Lu, PhD, Qi Gao, PhD, Ma Shwe Zin Nyunt, PhD, Tamas Fulop, PhD, MD,4 Christopher Pineda Monterola, PhD, Joo Chuan Tong, PhD,6, Anis Larbi, PhD, and Tze Pin Ng, MD,	2019	It is widely recognized that biological age (AB) most accurately measures the rate of human aging relative to declines functions than chronological age (BC), which simply measures the number of years since birth.
The biological age of the heart is consistently younger than chronological age	Sofia Pavanello, Manuela Campisi, Assunta Fabozzo, Giorgia Cibin, Vincenzo Tarzia, Giuseppe Toscano & Gino Gerosa	2020	People don't age at the same rate, and some of us age much more dramatically than others. Genetic and environmental factors can contribute to biological aging, which means that people can be affected differently, looking younger or older than their birth date would predict.
Biohorology and biomarkers of aging: Current state-of-the-art, challenges and opportunities	Fedor Galkin, Polina Mamoshinac, Alex Alipera, João Pedro de Magalhães, Vadim N. Gladyshev, Alex Zhavoronkova.	2020	The two concepts: chronological age and biological age (BC and BA) are intertwined and are sometimes used interchangeably in the literature, implicitly and explicitly. The definition of AC is trivial: the time elapsed since birth (or onset in the case of gestational age). Meanwhile, BA is a fluid and boundary placeholder concept used to refer to the time-dependent component of an organism's overall health condition and is often juxtaposed with CA. One might reasonably doubt the necessity of such a concept which creates semantic barriers.
Biological versus chronological aging	Magda R. Hamczyk, PHD,a,b,c Rosa M. Nevado, MS,a,b Ana Barettino, MS,a,b Valentín Fuster, MD, PHD,a,d Vicente Andrés, PHDa,b	2020	The observation that individuals do not age at the same pace led to the concept of biological aging, also known as functional or physiological aging. While chronological aging refers only to the passage of time, biological aging refers to decline in function.
Determination of Biological Age: Geriatric Assessment vs Biological Biomarkers	Lucas W. M. Diebel & Kenneth Rockwood	2021	Biological age is the concept of using biophysiological measures to more accurately determine an individual's risk of age-related adverse outcomes. This construct aims to provide a more orderly relationship between the individual's current state of health and their proximity to death.
Frailty and Biological Age	Lixin Ji, S. Michal Jazwinski, Sangkyu Kim	2021	Biological age is equivalent to physiological or functional age.
Analysis of Epigenetic Age Acceleration and Healthy Longevity Among Older US Women	Purva Jain, PhD, MPH; Alexandra M. Binder, ScD, ScM; Brian Chen, PhD; Humberto Parada Jr, PhD, MPH; Linda C. Gallo, PhD; John Alcaraz, PhD; Steve Horvath, PhD, ScD; Parveen Bhatti, PhD; Eric A. Whitsel, MD, MPH; Kristina Jordahl, PhD; Andrea A. Baccarelli, MD, PhD; Lifang Hou, MD, PhD; James D. Stewart, PhD; Yun Li, PhD; Jamie N. Justice, PhD, MS; Andrea Z. LaCroix, PhD	2022	Biological aging encompasses changes in the underlying hallmarks of aging, including epigenetics, which are associated with health trajectories and risk of morbidity and mortality.
Psychological factors substantially contribute to biological aging: evidence from the aging rate in Chinese older adults	Fedor Galkin, Kirill Kochetov, Diana Koldasbayeva, Manuel Faria, Helene H. Fung, Amber X. Chen, Alex Zhavoronkov	2022	We interpreted biological age as a parameter for general health status and showed that positive feelings (joy, hope, security) have a significant impact on the former.
Distinct biological ages of organs and systems identified from a multi-omics study	Chao Nie, Yan Li, Rui Li, Claudio Franceschi, Brian K. Kennedy, Xun Xu	2022	Biological age (AB) was developed to assess the true rate of aging and to counteract chronological age..
Source: Authors, 2023			

Table 3: Articles that discuss existing biological markers.

Article Title	Authors	Year	Marker	Definitions
Biohorology and biomarkers of aging: Current state-of-the--art, challenges and opportunities	Fedor Galkin, Polina Mamoshina, Alex Aliper, João Pedro de Magalhães, Vadim N. Gladyshev, Alex Zhavo-ronkov	2020	Telomere length	The variation in telomere length is seen as a strong biomarker, as it is a milestone that affects all individuals, with healthy behavior or not, since with each replication of cellular DNA, the telomere undergoes shortening, delimiting a maximum number of cell divisions and reducing the organism's regeneration potential,
			Biochemical com-pounds	The biochemical molecules present in the body, such as choles-terol, glucose, urea, calcium, can also be used as biomarkers of aging. In addition, r innovators, because using their results, can also measure the mortality risks of an individual through a clock that works through artificial intelligence (Aging. AI), where data from serological profiles of various blood tests are collected, building a database that correlates biochemical compounds and mortality risks.
			Epigenetic marks	When it comes to epigenetic marks, the information contained externally and internally in the DNA sequence is taken as a basis, such as promoter DNAs, enhancer DNAs, and proteins that form their structures, among others. However, the main relationship of epigenetic marks as biological markers is the DNA methylation process, and this process has been widely used in biogerontology as a measure of biological age.
Deep learning for bio-logical age estimation	Syed Ashiqur Rahman, Pedro Giacobi, Lee Pyles, Charles Mullet, Gianfranco Doretto, Donald A Adjeroh	2021	Anthropometry	Different anthropometric attributes are correlated with age and therefore, such measures can also be combined to estimate bio-logical age and their correlations with mortality, such as weight, height, BMI, arm length, abdominal circumference, skinfolds, waist-to-height ratio;
			Physical activity	Physical activity can be measured through the accelerometer device, which registers every minute for 7 days and, according to its intensity, can estimate the biological age. physical activity is also related to the cardiorespiratory system, which is also related to mortality levels
			Images	Some images have also been used to estimate biological age, such as brain MRI, a CNN-based network was used to estimate brain age in Deep Learning and showed that the age predicted by the brain represents a reliable phenotype that can be used as a biomarker
			Deep Learning	The use of artificial intelligence to profile an estimated biologi-cal age is already a reality through Deep Learning, this study is based mainly on three classes of measures to quantify in Deep Learning algorithms: physical activities, blood samples (bio-markers) and body shapes (anthropometry).
Source: Authors, 2023.				

The final sample of this review consisted of 32 scientific articles, selected by previously established inclusion criteria. Of these, eighteen (18) were from MEDLINE/PubMed, three (3) from the LILACS database, one (1) via SciELO and ten (10) via academic google. In the other databases, no qualified articles were found to fulfill the purpose of this study.

Discussion

The main themes displayed by the articles were: aging process and factors that promote it, "marks of aging", biological age and biomarkers for estimating biological age. The aging process is one of the main contributors to morbidity and mortality [12]. The course of this process is preceded by two main sources: genetics and interaction with the environment [13]. Biological age is a product of these sources and indicates the state of human aging regardless of the number of years that have elapsed, as time passes equally for all living beings, but physiological changes are governed by other magnitudes. The definition of biological age has been the subject of research for decades, seeking to determine the true rate of aging, as accurate information about it will favor the discovery of intervention goals to improve health and/or delay aging [14].

Biological age definitions have become increasingly specific through scientific advances. Initially, Hayflick established differences between chronological age and biological age [5] until, in 2022, they pointed to the possibility of measuring the marks left by the biological aging process [15]. Mechanisms that contribute to aging have been summarized under the term "marks of aging" and include eleven items: loss of proteostasis, mitochondrial dysfunction, altered nutrient sensing, telomere wasting, genomic instability, cell senescence, stem cell exhaustion, alterations epigenetics and alterations of intercellular communication.

Faced with so many markers, it becomes apparently complex to identify their levels of hierarchy and their practical viability. However, although this is the ultimate goal of any scientific development, there are essential factors for understanding these biomarkers, such as realizing that different measures of biological aging may not measure the same aging processes [16] and that the term biomarker is different from a clock biological, because while the first reflects changes in the organism at the molecular or cellular level over time, the second tends to be more of a generalization of the general state of the organism [17].

The large number of studies in search of the biological clock and biomarkers of aging show the need to measure biological age in human beings [8], since age, when measured chronologically, is no longer a reliable indicator of the rates of physiological degradation of systems and organs [2]. Research proposed that biological age be considered as subject to subjectivity, but with the advancement of science, the possibility of calculating it arose, being able to determine and explain the deficits between the average life expectancy of a population and the life expectancy perceived in an individual, leaving the field of hypothesis with the discoveries of biological markers [18]. In this integrative systematic review, the main markers of aging: 1. Telomeres; 2. Epigenetic marks; 3. Biochemical compounds; 4. Deep learning.

Telomeres

The accumulation of cellular damage can produce effects on the genome. Telomeres are regions prone to degradation with advancing age [19] and the shortening of their length is understood as a strong biomarker, as it occurs in all individuals at each replication of cellular DNA. Telomere exhaustion endorses the theory: "Hayflick limit and replicative senescence" [19]. Rapid telomere shortening is linked to female aging [15], risks of cardiovascular disease [20] and Alzheimer's disease [8]. Individuals in the age group of 60 years, with shorter telomeres, have a higher mortality potential than individuals with longer telomeres [8]. There are limitations in research related to telomeres, making their length not the main basis of a biological clock.

Epigenetic marks

Epigenetic alterations correspond to the study of structural modifications of the genome, whether by DNA methylation, chromosomal histones or other mechanisms that affect gene expression without altering the basic composition of DNA [8]. Epigenetic alterations do not constitute genetic inheritance, but regulatory mechanisms of genetics [21] and are used as biological age gauges because they correlate with the aging of the body and its relationship with various diseases, including obesity, blood glucose levels, and various causes of mortality [8].

Biochemical compounds

Small biochemical molecules, such as cholesterol, glucose, urea, calcium, are directly related to senescence [19] and can be used as biomarkers of aging. The first research based on blood biochemistry was carried out in 2016 [8] and became promising due to its ease of collection and financial accessibility, which could be used alone or complementing other analysis methods. In addition, they can be innovative, because using their results, they are able to measure the mortality risks of an individual through a clock based on artificial intelligence, where data from serological profiles of various blood tests are collected, building a database that correlate biochemical compounds and mortality risks [8].

Deep Learning

The use of artificial intelligence to profile an estimated biological age is already a reality through Deep Learning, a subfield of traditional machine intelligence, where not only data or algorithms are used, but several multiple and non-linear layers with information, as if it were an interconnected computational neural network. With its use, the estimated biological age can be useful in the process of tracing population health profiles and be an early indicator of the health status of some patients who may benefit from palliative care in the future, as a kind of monitoring that would be useful even for public policies aimed at the health network. This study is mainly based on three classes of measurements to quantify in Deep Learning algorithms: physical activities, blood samples (biomarkers) and body shapes [9].

Levine listed 5 main algorithms for estimating biological age and used the Klemera and Doubal (KD) method as the most reliable predictor to correlate with mortality. [9] Putin et al., 2016, used such markers in Deep Learning architecture, through multiple deep neural networks (DNNs) trying to assess the importance of each blood biomarker in this and they noted the five most important biomarkers that can estimate age human biological: albumin, glucose, alkaline phosphatase, urea and erythrocytes. Fischer et al [9], showed that these biomarkers are important to reveal, even in healthy people, the future risks of mortality in 5 years, with heart diseases, cancer and others, suggesting that the biomarkers can be related to aging and mortality rates.

Conclusion

Aging brings together the most complex combination of molecular, cellular and organic characteristics observed in organisms. With the rapid increase in older people across the world, it is a priority to develop automated ways to assess metabolic age to achieve successful aging. Biological age is a concept that a person's actual age may differ from their chronological age. It is often seen as the true age of an individual, providing a better measure of individual life expectancy. Biological age is referred to as physiological or metabolic age, seeking to assess how different organs, physiological processes and body regulatory mechanisms are functioning and to what extent they are stable.

No single biomarker appears to have a secure correlation with biological age. It is of great interest that there are reliable biomarkers to identify individuals who are vulnerable to loss of functionality due to age. Research includes immunological and inflammatory markers, DNA methylation, telomere length, among others, but studies involving the interaction of multiple pathways, practicality and low cost is the target of many of these researches. Biological age predictors using deep neural networks became public in 2016 and gained ground in biological aging and longevity research. Deep learning or Deep Learning is a Machine Learning

that employs algorithms to process data by imitating the processing done by the human brain (mathematical neurons).

Machine learning approaches are rapidly becoming a pervasive tool in all areas of science and will undoubtedly be essential for developing interventions against most chronic diseases and perhaps the aging process itself.

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Conflict of interest

None.

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