Biomarkers associated with early detection of aging in human: a review

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Abstract –

Most chronic illnesses as well as functional deficits happen to be exacerbated by aging. There happens to be an existing significant heterogeneity inside of the level that belongs to illness as well as functional impairment risk within an existing homogenous age group, highlighting the need that is going to belong to appropriate biomarkers to help inside of describing the complicated aging processes. The diversity that belongs to biological living environments, lifestyle activities, as well as medical treatments complicates the discovery that belongs to biomarkers even further. During the same time as an existing result, no one biomarker or gold standard instrument that is going to belong to monitoring effective or healthy aging has been identified. The current state that belongs to knowledge on top of possible biomarkers happens to be described inside of this brief overview, with an existing emphasis on top of their application to the primary physiological systems influenced by the aging process, such during the same time that physical capacity, nutritional status, body composition, as well as endocrine as well as immunological function.

Keywords *- Biomarkers, Aging, MARK-AGE consortium, biomarkers of different human organ systems, frailty syndrome biomarker, DNA methylation biomarker, Phenotypic biomarker, Genetic biomarker, Immunological biomarker, Cellular biomarker, Deep - Aging clocks*

BACKGROUND

A. What is Aging?

Although most scientists still attempt to differentiate between normal aging and that due to disease, scientists related to public health are observe the age-related health changes minutely that are of interest in evaluating functional ability and survival, which typically represent some combination of aging and disease. Verbrugge and Jette has refered to alterations in health at old age as the disablement process [1,2].

Health changes in an expected occurrence among populations with aging, starting with the formation of risk factors, progressing through the onset of diseases and conditions, to loss of function or loss of ability to perform physiological functions as expected, and eventually leading to the development of various disabilities, that is often indicated by inability to work, look after oneself, or perform the activities needed for the freelance living among older populations. Frailty may be a new term developing within the public health study in older folks [1]. Deterioration in health and capability to perform everyday duties caused by the buildup of acute and chronic illnesses; still, because of the physiological decline and dysregulation that accompanies sickness and late age [2]. Biomarkers are indicators of changes in individual health, together with risk, illness, practical loss, disability, frailty, or close-at-hand mortality [2].

B. What is a Biomarker?

A biomarker may be attributed as a component to be evaluated systematically as an indicator of traditional biological processes, morbific processes, or pharmacologic responses to a therapeutic intervention. the present stress on biomarkers is actuated by a want to raise perceive the molecular and physiological roots of sickness, as well as assess therapeutic interruptions victimizing surrogate endpoints instead of death or irreversible sickness [3]. Biomarkers are utilized in populations to watch and forecast population health, determine folks with special hindrance or vulnerability to health issues, and assess treatment interventions. Because of the clinical attribution of the term "biomarker" with the danger factor, one cluster specializing in aging populations has coined the phrase "bio measure" as a higher-order term to hide biomarkers of organic illness, physical condition, or function, genetic markers, and biological indicators of aging [1,4].

Many molecular and cellular mechanisms are connected to aging and contribute to its makeup in recent years. Scientists anticipate nine aging characteristics which will be characterized as main, antagonistic, or integrative. The foremost hallmarks are important mechanisms that cause cellular damage, akin to genomic instability, end attrition, proteostasis loss, and epigenetic changes [4].

MAIN TEXT

I. CRITERIA FOR BIOMARKER OF AGING

According to the American Federation for Aging Research (AFAR), a biomarker of aging should fulfill the following criteria:

1. It should predict exactly where a person is their total life span and it must predict human life span in a better fashion than their chronological age.

2. It must be able to track a basic process that underlies the process of aging, and not the disease-effects.
3. The biomarker must have the ability to be tested repeatedly without causing any harm to the person, for instance, an imaging technique or a blood test.
4. It must work in both humans and laboratory animals, such as mice, so that it can be tested in lab species before substantiated in humans [5].

II. MARK-AGE CONSORTIUM

The MARK-Age Consortium was born out of the need to address the scientific concerns associated with establishing powerful biomarkers of human aging. It incorporated 26 partners consisting of 21 non-profit organizations, 3 small and medium sized enterprises and 2 large companies. Several scientific groups which are at the forefront of aging science research are associated with MARK-Age Consortium. Also, some partners are International leaders in the fields like Genetics, etc. High amount of interdisciplinary is a characteristic feature of MARK-AGE Consortium: The assembly of competence ranged from Biochemistry, Genetics, Geriatrics, Immunology, Bioinformatics, etc. For any project to be successful, this level of interdisciplinary is absolutely necessary [6,7].

III .BIOMARKERS OF DIFFERENT SYSTEM OF THE HUMAN BODY

A. *CARDIOVASCULAR SYSTEM* - One of the main reasons of death in the elderly is heart disease and it is also one of the primary causes of disability. The two biomarkers for blood pressure which are most extensively tested are:

i. Systolic blood pressure (SBP) – It is the maximum pressure in an artery during the process of beating and pumping of blood by heart.

ii. Diastolic blood pressure (DBP) – It is the minimum pressure in the artery while the heart is resting between beats

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ii. Diastolic blood pressure (DBP) – It is the minimum pressure in the artery while the heart is resting between beats [1,8].

Hypertension is indicated by high values of either measurement. SBP is thought to be a better predictor of aging health outcomes than DBP. Aging elevated SBP, and cardiac and vascular disorders all have substantial links. SBP has been found in studies to have a greater prognostic potential for coronary heart disease and life expectancy at advanced ages [8].

Some academics choose to utilize pulse pressure (PP) as an alternate parameter when examining aging. The increase in SBP and PP in middle-aged and older people is mostly due to increasing large-artery stiffness and an increase in wave reflection amplitude. SBP and DBP alter equally during middle age; however, after the age of 60, DBP falls while SBP continues to rise, resulting in a significant increase in PP in old age. While risk factors such as smoking, lack of physical activity, and drinking influence PP, studies have shown that PP

has an independent effect on health outcomes when these risk factors are controlled for. A pulse rate of 90 beats per minute or more is considered high and is linked to an elevated risk of CHD, as well as cardiovascular, noncardiovascular, and all-cause mortality [1,8].

B. METABOLIC PROCESSES - Cholesterol performs various activities, including maintaining cell membrane integrity and assisting in the creation of steroid hormones and bile acids. For the evaluation of the likelihood of heart disease, the following elements of total cholesterol are frequently analyzed: LDL (Low density lipoprotein), HDL (High density lipoprotein), and VLDL (Very low density lipoprotein). It has been found that Total cholesterol level have a direct connection with CHD and are the reason of death in middle-aged populations [1].

Due to its proven link to CHD, coronary atherosclerosis, and mortality risk, LDL is commonly referred to as "bad" cholesterol. According to current standards, a good amount of LDL cholesterol is less than 130 mg/dl. LDL cholesterol levels should be fewer than 70 mg/dl in patients with cardiovascular disease and diabetes. VLDL levels, like LDL, rise with age and are usually referred to as "bad" cholesterol [1,9]

Elevated levels of High density lipoprotein (good cholesterol) provides protection against heart disease by conducting cholesterol from the arteries to the liver. In the liver it is excreted. Traditional lipid measures like total cholesterol and HDL are often utilised freely to depict lipid profiles and how they are related to health outcomes. However, studies have proved that the total cholesterol/HDL ratio can also be used as a biomarker which is related to other cardiovascular peril factors and indicates the dangers of atherosclerotic plaque rupture and ischemic heart disease [9].

High levels of triglycerides, a sign of stored fat, have been linked to heart attacks, CHD, and coronary artery disease.

Diabetes and prediabetes are indicated by fasting blood glucose levels. Some studies demonstrate that HbA1c increases with age, while others show little or no increase with age, presumably because of its association with mortality [1].

Anthropometric parameters that may be utilized to govern adiposity and weight are BMI (Body Mass Index), waist-to-hip ration (WHR), weight and waist and hip circumference. It has been established that BMI & WHR have a direct connection to adult-onset diabetes, different types of cancer, hypertension, heart disease, atherosclerosis decreased aerobic capacity, osteoarthritis and muscular strength, and disability [9].

Leptin is a hormone that is crucial in the long-term control of body weight. Leptin is implicated in the physiology of many disorders because it is a critical regulator of food intake and energy balance. Leptin secretion is altered in old age due to reductions in organ function and changes in hormone production. Several studies have suggested that leptin may have an essential role in a variety of chronic disorders, including metabolic syndrome, atherosclerosis, malnutrition, type 2 diabetes, dyslipidemia, hypertension, osteoarthritis, and osteoporosis [1,9].

C. CENTRAL NERVOUS SYSTEM - Several putative indicators for Alzheimer's disease (AD) from cerebrospinal fluid (CSF), for example, Amyloid 42 is a proposed sign of neuropathological processes connected to AD [1]. Total (t)-tau, a key protein in the creation of neurofibrillary tangles, and phosphorylated (p)-tau that occurs before the formation of neurofibrillary tangles is directly linked to an increased risk of Alzheimer's disease. F2-

isoprostanes (F2-iso), prostaglandins that indicate lipid peroxidation is also linked to Alzheimer's disease, hypercholesterolemia, and atherosclerotic plaque [1,10].

D. HYPOTHALAMIC PITUITARY ACTIVITY - A steroid hormone named cortisol is produced by the adrenal cortex in response to internal or external stress. Abnormal cortisol reactivity to frequent stressors is an unusual reaction that could be an indication of persistent physiological stress and it has a connection to poor health consequence in elderly. Notable HPA activity biomarkers are cortisol and its antagonist dehydroepiandrosterone sulfate markers [11].

Blood, saliva, and urine can all be used to measure cortisol levels. DHEA, an adrenal gland hormone, synthesizes DHEA-S and converts it to other hormones. DHEA-S is measured by assays because of its fast elimination from the circulation and little diurnal fluctuation. DHEA levels increase with aging, with its production ceasing at birth, returning at the age of seven, and peaking in the mid-twenties [11].

Insulin-like growth factor-1 (IGF-1) is a polypeptide protein hormone which causes the regulation of cell survival and cell development. It affects neuronal shape and function during the entire lifetime, most commonly by its influence on GH (Growth Hormone). A connection between high IGF1 levels and elevated chances of prostate cancer and premenopausal breast cancer has been established. Also. Low IGF1 level has been found to be linked with higher mortality, osteoarthritis and coronary disease. But, according to a recent study by the nationally-representative NHANES, no link between low IGF1 and all-cause mortality, cancer mortality or heart disease mortality has been found [12].

E. *OXIDATIVE STRESS AND ANTIOXIDANTS* - Oxidative stress and antioxidants that are necessary determinants of aging are examples of class of indicators. Elevated amount of reactive oxygen species (ROS), and enzymes responsible for cell signaling, have been found to destroy cell structures. ROS has important roles in the start in the commencement of age-related muscle mass loss, alter the CNS, loss of hearing, Parkinson’s and Alzheimer’s. On the contrary, intrinsic antioxidants like SOD (superoxide dismutase) and glutathione peroxidase as well as extrinsic antioxidants like vitamins A, B, C & E regulates aging and illness by retaliating oxidative stress.

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According to research, SOD may act as a tumor suppressor, whereas carotenoids may protect against both cardiovascular disease and cancer [1,13].

IV. FRAILTY SYNDROME AS AGING BIOMARKER

Frailty is an important geriatric syndrome that is portrayed by an age-associated reduction in physiologic functions across multi-organ systems. It leads to increased vulnerability to unfavorable health issues. The frailty phenotype characterizes frailty as a specific clinical

syndrome that meets three or more of the five phenotypic criteria: slowness, self-reported exhaustion, weakness, low level of physical activity, and unintentional weight loss [14]. Older individuals in whom none of these five characteristics are found are classified as non-frail [15].

Over the past decade, two major definitions have surfaced with proposed assessment tools. These are

1. The frailty phenotype (FP) is also called Fried's definition or Cardiovascular Health Study (CHS) definition [15].
2. The frailty index (FI) [16].

Frailty has been found to increase significantly in humans during aging, and thus it has been examined as a target for anti-aging interventions. In some of the studies, like the one conducted by Palliyaguru and his colleagues, aspects of the mouse frailty index have been used for the purpose of quantification of the efficacy of anti-aging interventions in vivo [17].

V. DNA METHYLATION BIOMARKERS IN AGING AND AGE-RELATED DISEASES

With age, a non-stop accumulation of epigenetic versions takes place in human beings, which may result in numerous health problems related to age. It has been disclosed in several epidemiological research that monozygotic twins explicit a heightened charge of phenotypic disharmonies, especially for age-associated sicknesses for older siblings [18,19]. A sluggish depletion in methylation conservation values with the next molecular divisions is probably a reason for this. This phenomenon is referred to as Epigenetic Drift [20,21]. This concept indicates an uplifted value of presumptive methylation mistakes at some point in the method of getting aged throughout the complete genome. It has been proved from numerous reviews that older monozygotic twins possess international variations in samples of DNA methylation in the assessment of more youthful individuals [22,23,24].

Vanyushin et al had been the chief to provide an explanation for 5-methylcytosine versions at some point of getting old in rats in 1973 [25]. To date, DNA methylation modifications that occur with an increase in age throughout more than one species had been discovered with the aid of using massive literature. Age-associated epigenetic changes may emerge systematically or are probably confined to a particular molecular or tissue type. These age-associated DNA methylation modifications also can be visible in germ cells and may in all likelihood be transmitted to the offspring [26, 27]. A new technology in epigenetics and advanced age-related studies was brought up with the aid of Steve Horvath. He made a multidimensional age predictor on the premise of DNA methylation values of CpG sites in 353 humans [28]. The Horvath clock is able to predict age comprehensively in all human tissues and molecular sorts besides sperm, while different clocks can simplest be used for a single tissue [29]. Recent research on the genome-extensive affiliation depicted tissue-precise correlation of editions in the immune system, metabolism, autophagy, and age-associated genes with an epigenetic acceleration of age [30, 31, 32, 33].

VI. PHENOTYPIC BIOMARKERS

There are a few phenotypic biomarkers of aging. However, the two most practicable phenotypic biomarkers are Physical function and Anthropometry. Considering this, the well-known measurements are - standing balance, walking speed, BMI, circumference of waist, muscle mass, etc. These physical functional measurements are straightforward but are found to outperform DNA methylation when it comes to predicting health status [34].

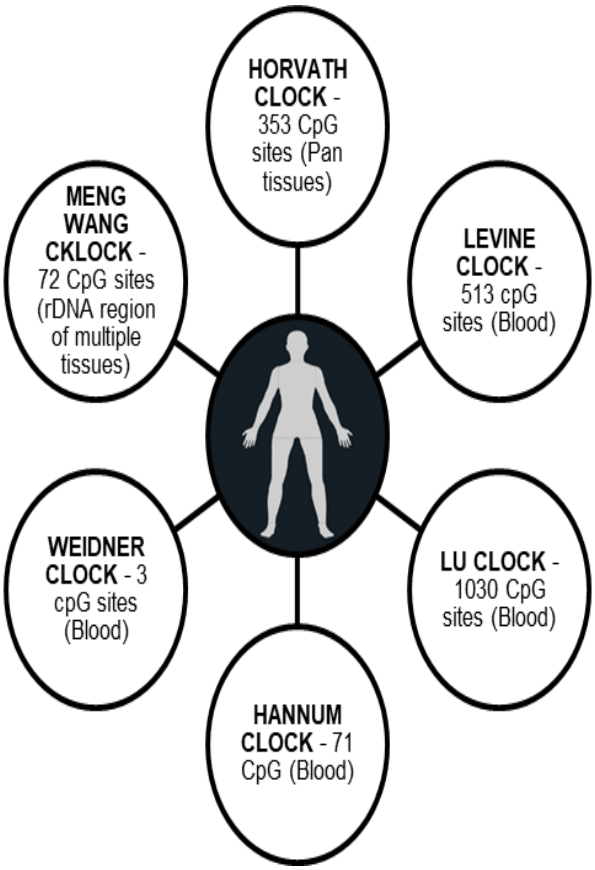

Fig 1 The growing number of epigenetic age timepieces developed for humans, including the number of CpG spots comprising the age- vaticination model, as well as the apkins in which age can be estimatedb

Quantitative phenotypes of exterior human traits are also associated with aging. Quantified face traits derived from three-dimensional (3D) facial photographs, such as mouth width, nose width, and eye corner droop, are strongly related to age. In reality, utilizing cutting-edge computer methods, 3D face pictures may be utilized to calculate an individual's biological age [26,35].

VII. GENETIC BIOMARKERS

A genetic marker is another kind of marker this is the handiest now being utilized in populace studies. The capability to appoint those markers is now no longer handiest as new impartial danger signs, however additionally as danger modifiers for humans with different behavioral, biological, or genetic developments could widen the general technique to the use of

biomarkers in populace fitness consequences analyses. To present, only some genetic markers had been broadly hired in populace studies, and the outcomes for a few of the signs have now no longer been as simple as anticipated given the animal literature, main to their identity as applicants for genes impacting human fitness and longevity [1].

Apolipoprotein E (APOE), the most regularly studied genetic biomarker with an apparent courting to fitness outcomes, has been hired within the research of the identical in several populations. Those with the APOE4 gene have a better risk of late-onset Alzheimer's disease, in addition to a hyperlink to cardiovascular illness (stroke, coronary heart attack, coronary artery disease) [1].

Polymorphisms within the gene encoding angiotensin-changing enzyme (ACE) have also been discovered to have a connection with Alzheimer's disease, coronary heart disease, and human longevity in numerous populace surveys [1].

Mitochondrial polymeric (mtDNA) mutations are known to increase with age and are one of the genetic variables which will be coupled to longevity in the near future. One analysis showed a relationship between lifetime and therefore the C150T mutation in leukocytic mtDNA, whereas another discovered a specific association between longevity and the C150T mutation in leukocytic mtDNA. Yet another study discovered that centenarian controls consisted of a few additional mtDNA than non-centenarian controls [1].

The end length of telomere is another genetic signal that's currently being studied as either a risk issue or a biological marker of the aging process. Though discoveries have systematically reciprocally linked end length to age, study results on the relation between telomere length and remaining longevity haven't shown consistency [1].

VIII. CELLULAR BIOMARKERS OF AGING

The proliferative potential of normal human fibroblast-like cells declines with aging. Cultures eventually become senescent and incapable of reproducing. Loss in proliferative ability is characterized by a decreasing proportion of cells synthesizing DNA in a given period, increasing cell cycle duration, and a decreasing saturation density. These parameters were both connected to the percent lifetime completed regularly and consistently and measured retrospectively by cell counts at each sub-cultivation till phase-out. As a result, these two measurements serve as independent biomarkers for cell culture aging since they are related to a single functional parameter—proliferative capacity, and thus, may be used to determine functional as well as chronological age [36].

IX. IMMUNOLOGICAL BIOMARKERS

It is a fact that with onset of aging a person becomes more susceptible to infectious diseases, autoimmune diseases and various types of cancers. This is an indication of the immune system becoming less competent and the deployment of greater influence on age-related mortality as well as morbidity. The functioning of the immune system has been found to be a great marker of health. Numerous alterations related to aging have been found to be connected to longevity of an individual [37,38].

Several studies on the role of aging on the immune system of the body clearly depict its effect on the compartment of the T cells. Age-associated thymic involution causes a gradual reduction in the production of naive T cells in the aged people. Also, a significant increase in memory T cells and a reduction in proliferation of lymphocytes and IL-2 generation have also been studied. Numerous changes in the functions of NK cells with the onset of aging have been explained in both humans and animals, however, the investigations have not been done in the context of Cytomegalovirus (CMV). Good functioning of NK cells in elderly people is absolutely essential because according to data, reduced NK cells is related to an increased chance of infectious diseases in humans as well as mice [39,40,41].

X. DEEP AGING CLOCKS: The Emergence of AI-Based Biomarkers of Aging and Longevity

A. Deep Blood Biochemistry and Cell-Count Aging Clocks

The knowledge that aging-related changes may be recorded has prompted the quest for a physiologically relevant data type with a large number of historical datasets as well as a limited number of highly variable but standardized attributes that can be readily anonymised [42]. The first aging clock research employing deep neural networks (DNNs) was published in 2016 by the laboratory of Zhavoronkov using one of the largest panels of regular blood tests done in different nations in a uniform manner. The researchers used over one million clinical blood tests (blood biochemistry and cell count) to produce a dataset of over 60 000 generally healthy patients annotated with sex and age from standard screening tests [39]. The proof-of-concept research proved the fundamental application of assessing the important contributions of each simple characteristic to the predictor's accuracy. The large amount of blood biochemistry data enabled for comparison of the various Machine Learning (ML) models, and the DNNs clearly outperformed in all tests [39, 43, 44, 45, 46].

The deep hematological aging clock project was expanded to include several million subject data in order to assess the demographic specificity and biological significance of these clocks in diverse populations, as well as the relationship between anticipated age and death [47]. The three DNNs were trained using anonymised Korean, Canadian, and Eastern European blood test samples annotated with age in this study [41]. When Korean and Eastern European data were tested with a DNN trained on Canadian data, Koreans seemed much younger than their chronological age, but Eastern Europeans appeared significantly older, revealing demographic disparities [48]. Furthermore, researchers discovered that persons expected to be older had greater death rates than those anticipated to be in line with their chronological age, supporting the biology and implying clinical implications of the clock [49].

B. Deep Imaging Aging Clocks

The Deep Imaging Aging Clocks utilizes only images of the corner of the eyes and predicts the age of any person. Its accuracy is found to be 1.9 years mean absolute error. In Spite of the photographic data lacking biological relevance, several phenotypic as well as genetic can be diagnosed using this. It has been observed that for numerous applications, images prove to be of greater value than genomic data. A research group at Haut.AI, an organization that specializes in digital skin analysis, has been studying these images [49,50,51].

C. *Deep Transcriptomic Aging Clocks*

Transcriptomic data are present in ample amounts but they are variable. The first transcriptomic aging clock was made in 2018 by utilizing Deep Learning (DL) and many other ML techniques. It was developed by using gene expression data from muscle tissue. This brings forth many ideas on how some definite gene could be given priority as potential targets for the purpose of pharmaceutical intermediation in cases of sarcopenia and different muscle-wasting diseases [51,52,53].

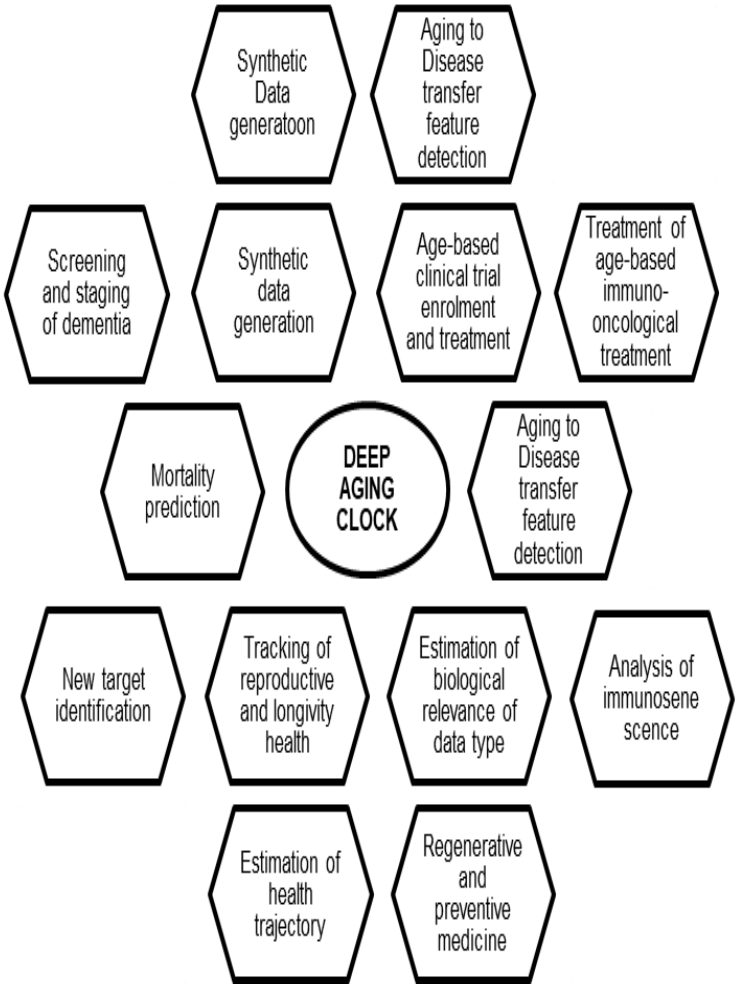

Fig 2 Prospective operations of Deep Aging timepieces in the Pharmaceutical and Biotechnology diligence

CONCLUSION

As expected given the intricacy of the ageing process, ageing biomarkers are deep and complex; encompassing a surprising number of components. While all factors may be relevant in the biological process of ageing, not all have been proved to be significant in evaluating human ageing at this time.

The MARK-AGE project was recently initiated as a huge-scale integrated analysis geared toward discovering a robust assortment of biomarkers for human aging victimizing over 3,200 people. Though more specifics concerning this initiative are nevertheless to be revealed, the speed with that the biomarkers of aging are known and accustomed to enhance human health, avoid aging-related disorders, and extend a healthy time period is accelerated by the huge quantity of knowledge gathered. This includes not simply data from major human cohort studies, but additionally normal people's genetic, purposeful genomic, phenotypic, and lifestyle data, which can be power-assisted by ever-increasing data capture, storage, and process capability. it's not impossible that sooner or later a synthetic intelligence laptop would be ready to predict how long someone can live supported by quantitative measurements in an exceedingly Brobdingnagian panel of aging biomarkers.

DECLARATION

A. *Abbreviations* –

- AFAR – American Federation for Aging Research
- SBP – Systolic Blood Pressure
- DBP – Diastolic Blood Pressure
- PP – Pulse Pressure
- CHD – Congenital Heart Defects
- LDL – Low-Density Lipoprotein
- HDL – High-Density Lipoprotein
- VLDL – Very Low-Density Lipoprotein
- BMI – Body Mass Index
- WHR – Waist-to-Hip Ratio
- AD – Alzheimer’s Disease
- CSF – Cerebrospinal Fluid
- F2-iso – F2-isoprostanes
- DHEA-S – Dehydroepiandrosterone Sulfate
- HPA – Hypothalamic–Pituitary–adrenal
- IGF-1 – Insulin-like growth factor-1
- GH – Growth Hormone
- ROS – Reactive Oxidative Species
- SOD – Superoxide Dismutase
- FP – Frailty phenotype
- CHS – Cardiovascular Health Study
- FI – Frailty Index
- NHANES – National Health and Nutrition Examination Survey
- CpG – 5'—C—phosphate—G—3'
- APOE - Apolipoprotein E
- ACE – Angiotensin-converting Enzyme
- mtDNA – mitochondrial DNA
- NK cell – Natural Killer cell

- CMV – Cytomegalovirus
- DNNs – Deep Neural Networks
- ML – Machine Learning
- DL – Deep Learning

B. *Ethics approval and consent to participate* –

This criterion is not applicable for this particular review study.

C. *Consent for publication* –

This criterion is not applicable for this particular review study.

D. *Availability of data and material* –

All data and material in this review article has been referred from open access research papers and review articles whose references have been listed below.

E. *Competing interests* –

On behalf of all authors, the corresponding author states that there is no conflict of interest.

F. *Funding* –

This criterion is not applicable for this particular review study.

G. *Acknowledgements* –

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