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Biomarkers of Human Aging

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Healthy Ageing and Longevity

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Series Editor

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Rapidly changing demographics worldwide towards increased proportion of the elderly in the population and increased life-expectancy have brought the issues, such as "why we grow old", "how we grow old", "how long can we live", "how to maintain health", "how to prevent and treat diseases in old age", "what are the future perspectives for healthy ageing and longevity" and so on, in the centre stage of scientific, social, political, and economic arena. Although the descriptive aspects of ageing are now well established at the level of species, populations, individuals, and within an individual at the tissue, cell and molecular levels, the implications of such detailed understanding with respect to the aim of achieving healthy ageing and longevity are ever-changing and challenging issues. This continuing success of gerontology, and especially of biogerontology, is attracting the attention of both the well established academicians and the younger generation of students and researchers in biology, medicine, bioinformatics, bioeconomy, sports science, and nutritional sciences, along with sociologists, psychologists, politicians, public health experts, and health-care industry including cosmeceutical-, food-, and lifestyle-industry. Books in this series will cover the topics related to the issues of healthy ageing and longevity. This series will provide not only the exhaustive reviews of the established body of knowledge, but also will give a critical evaluation of the ongoing research and development with respect to theoretical and evidence-based practical and ethical aspects of interventions towards maintaining, recovering and enhancing health and longevity.

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Chapter 1
Introduction

Alexey Moskalev

Abstract In laboratory studies, potential geroprotective interventions have been created: more than 400 geroprotectors, several gene and cell therapies. Their translation into medical practice is restricted, in part, due to the inability to assess clinical efficacy. Human biomarker panels are needed. Based on them, it will be able to predict the accelerated or delayed aging of an individual, track the effectiveness of procedures aimed at preventing aging, such as changing diets, lifestyles, increasing physical activity, geroprotective drugs. Aging biomarkers are an integrative qualitative and quantitative indicator of the functional state of a person and this is their key difference from the risk factors of specific age-related pathologies (type 2 diabetes, cardiovascular diseases, Alzheimer's or Parkinson's). In other words, aging biomarkers are indicators of a preclinical stage of father aging-related pathologies. Interventions should reverse these biomarkers to a younger state or slow down their changes with aging.

Keywords Aging biomarker · Biological age

Aging is the result of the destructive impact of metabolic errors and external stress factors on the individual development of the body, expressed in compensatory hyperfunction and failure of systems for maintaining homeostasis (from molecular to organismic levels) and increasing the likelihood of illness and death in life-compatible conditions.

The rate of aging in different people of the same age may distinguish significantly. They vary for different systems and organs within the same organism. The aging of one system causes changes in many others. For example, aging of the cardiovascular system may contribute to neurodegeneration and cognitive impairment, diseases of the liver and kidneys. Metabolic syndrome affects the aging of the immune system.

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Thus, in addition to the passport age (calendar, chronological), each person has a biological age, determined by the individual rate of aging. The rate of aging depends on the genetic characteristics of a person, and to a large extent, on the interaction of environmental factors with systems for maintaining homeostasis of the internal environment of the body, epigenetics.

When talking about the rate of aging, in classical biogerontology, as a rule, it means a change in the average and maximum lifespan of model animals. However, a person's life expectancy is so long that exploring the indicators of its longevity under the influence of lifestyle, diet, various drugs, gene and cell therapies is long and expensive. Therefore, the idea arose to identify the relationship with age of various physiological and metabolic changes, monitoring of which would help in assessing the effectiveness of anti-aging therapy.

The physiological norm adopted in modern medicine for many indicators changes with aging. This creates the prerequisites for observing and measuring age deviations. At the same time, the level of stochasticity (randomness) of deviations increases, which makes it difficult to interpret data on the rate of aging.

Biomarkers of aging are molecular, cellular and physiological parameters of the body that demonstrate reproducible quantitative or qualitative changes with age. Ideally, anti-aging interventions should reverse these biomarkers to a younger state or slow down the changes with aging.

Biomarkers of aging have great potential for early diagnosis and prognosis of the development of chronic age-related diseases, as well as monitoring the effectiveness of their prevention and treatment. Aging biomarkers are a common qualitative and quantitative indicator of a person's functional state and this is their key difference from the risk factors of specific age-dependent pathologies (type 2 diabetes, cardiovascular diseases, Alzheimer's or Parkinson's). In other words, aging biomarkers are indicators of preclinical stage of father aging-related diseases.

Many age-related pathologies develop for a long time in a latent form. In the early stages of the development of the disease, its clinical manifestations are nonspecific, that is, common with other age-related changes. In this case, the earlier such deviations from the norm associated with the risk of a specific disease are detected, the more effective prevention is, the more likely it is success in preventing life-threatening conditions.

The following main criteria for aging biomarker were proposed (Butler et al. 2004):

- Must change with age;
- Have to predict mortality better than chronological age;
- Allow foreseeing the early stages of a specific age-related disease;
- To be minimally invasive—do not require serious intervention or painful procedure.

We extended the list by additional criteria, that could increase their translation potential:

- To be sensitive to early signs of aging (as opposed to frailty and mortality, which are too late for prevention and geroprotection);

- Have predictability with collecting in the foreseeable time range;
- Have low analytical variability (robustness and reproducibility).

The most comprehensive online database of human aging biomarkers today is Digital Aging Atlas (http://ageing-map.org) (Craig et al. 2015).

Based on them, we can predict the accelerated or delayed aging of an individual, monitor the effectiveness of procedures aimed at preventing aging, such as changing diet, lifestyle, increasing physical activity, the effectiveness of geroprotective drugs.

The most generally accepted classification of existed biomarkers relies on the level of organization: molecular, cellular, physiological, psychological.

There are 3 different experimental approaches to develop new aging biomarkers:

1. *Empirical*. Search for significant correlations with age among a variety of physiological, clinical and biochemical parameters. The advantage of the approach is that the methods underlying it are already used in clinical practice. This approach has maximum translational potential and minimum cost.
2. *Aging mechanisms oriented*. Search for predictors of aging among changes associated with known aging mechanisms. Since the approach is based on one of the hypotheses about the causes of aging, it is difficult to confuse the cause with the effect or to base on the false correlation between parameter and age. However, there is always a chance that this is not the main reason of aging. In this case, the variability of the index will be great, and the predictive power is minimal.
3. *Omics*. Analysis of age-related correlates among the big data obtained from the analysis of various "omics": genome, epigenome, transcriptome, metabolome, proteome, microbiome. The main advantage of this approach is we can assume that not really know anything about the causes of aging nowadays and analyze all possible data of the person.

While there are no single definitive biomarkers for aging, that reflect of the all necessary criteria, a range of different measures have been proposed. In different organs and systems, aging processes occur at different times and at different speed. Thus, aging biomarker should be multimodal panel, based on different molecular and physiological parameters.

Analysis of the results of the study of the National Research Center for Preventive Medicine and the Russian Gerontological Scientific and Clinical Center, in which 303 people aged 23–91 was assessed according to 89 parameters, allowed us to make a rating of the predictive power of the parameters studied, including telomeres length levels of certain hormones, inflammation factors, blood metabolites, anthropometry and functional tests. However, the most important predictors of age were vascular health parameters (central arterial pressure, augmentation index, degree of stenosis, vessel wall thickness, pulse wave velocity) (Fedintsev et al. 2017). The biological age values obtained according to our model, as expected, were significantly higher in people with diabetes and hypertension than in healthy people.

We investigated more than 60,000 results of a general analysis of blood and extensive blood biochemistry using deep machine learning methods. The study created a universal model of biological age Aging.AI where most predictive parameters were

albumin and alkaline phosphatase (liver function), glucose (metabolic syndrome), erythrocytes (respiratory function) and urea (renal function) (Putin et al. 2016).

DNA methylation "epigenetic clock" is the most comprehensive predictor of total mortality today. It is also can predict mortality from cancer and cardiovascular diseases and vary in correlation with lifestyle and interventions (Quach et al. 2017).

In this book for the first time collected all advances in the area of human aging biomarkers. The accumulated data is quite enough to assess the rate of aging of the patient and individually monitor the effectiveness of therapies aimed at slowing aging. We need to do next big step, translating this knowledge into clinician practice.

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Part I
Biomarkers of Aging and Health

Chapter 2
Practical Detection of Biological Age: Why It Is not a Trivial Task

Boris Veytsman, Tiange Cui and Ancha Baranova

Abstract The determination of the "biological age" is one the most interesting problems in the biology of aging. The improvement of the biomarkers of aging is a very important problem. The necessity to use synthetic (i.e. holistic), rather than analytic (i.e. specific) measurements strongly contributes to a deeply complicated relationship between conventional biomedicine and a plethora of anti-aging interventions which are inferred from experimental studies of animals and observational studies of humans. Intrinsically holistic "omics" profiles, however, are subject to the "curse of dimensionality", discussed in this chapter. It is expected that an increase in the reliability of biomarkers of aging would be achieved by concerted efforts of biostatisticians, who would successfully combine data-driven and knowledge-based approaches, and the biologists who would be instrumental in critically evaluating insights generated in silico and ensure a discernible biological rationale for the metrics of biological age.

Keywords Biological age · Biomarkers · Curse of dimensionality · Omics · Holistic measures

One of the most interesting problems in the biology of aging is the determination of the "biological age", which might be a better predictor of the person's health state than the calendar age. Accordingly, biological age is often imagined as a holistic metrics describing the person as a whole rather than reflecting the functioning of the body

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through one or another representative parameter, or a combination of a relatively small number of such parameters. The goal to describe the process of aging as a whole firmly places the studies of aging into a systems biology realm (Yashin and Jazwinski 2015). On the other hand, the necessity to use the synthetic (i.e. holistic), rather than the analytic (i.e. specific) measurements strongly contributes to a deeply complicated relationship between conventional biomedicine and a plethora of anti-aging interventions which are inferred from experimental studies of animals and observational studies of humans.

To give some meaning to the concept of biological age let us imagine the process of aging as a trajectory in a multidimension space, each dimension being some measurable characteristics of the body's function or performance. These trajectories vary between individuals. Moreover, each individual follows the trajectory with a specific velocity, which may accelerate or decelerate depending on specific circumstances encountered along the trajectory. If we assume that each trajectory could be mapped in a set of natural coordinates known as a panel of biomarkers, we are able to compare the points on a given set of trajectories. Moreover, we are able to compare individuals and to check how far each of them is along the way; to understand why the velocity along the trajectory changes, and how is the trajectory itself determined.

It is further assumed that the biomarkers, or, to be specific, the levels of these biomarkers, which are used as indicators of the position along the trajectory, are objective. It is important to remember that objectivity here is no more than assumption which relies on one or another underlying theory of aging, or a combination of theories. One relevant example showing that the objectivity of biomarkers is relative is the famous aging-related measure of telomere length, commonly used as an integrative biomarker of stressful exposures and increased propensity to develop chronic disease or succumb to early mortality. Despite the telomere's popular designation as a mitotic clock, the relationship between telomere length and aging does not meet the requisite biomarker criteria (Mather et al. 2009). One of the four criteria for biomarker of aging proposed by the American Federation of Aging Research posits that a potential biomarker should be allow repeated testing without harming the subject (Simm et al. 2008). A blood test or an imaging test would satisfy this requirement. Accordingly, telomere length is most commonly profiled in peripheral blood mononuclear cells (PBMCs), that may be collected during routine venipuction. PBMCs, however, are far from being an uniform tissue; they represent a heterogeneous mixture of cell types of different physiological ages. Accordingly, these cells may have different telomere lengths (Lin et al. 2015, 2016). As the proportions of the cells in the mix may vary depending on state of the body (for example, reflecting underlying infection processes and stage of body recovery), average telomere length may fluctuate. Moreover, PBMCs composition may change with the process of aging itself (Aviv et al. 2006). Finally, the average telomere length in PBMCs may not correspond to telomere length in other tissues (Palmieri et al. 2014), may not be uniform in various human populations of the same age (Eisenberg et al. 2011), and may not accurately reflect regeneration potential of the cellular compartment (Böttcher et al. 2018). Taken together, these considerations