

# Beyond Personalized Medicine: Personalized Lifestyle

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## Introduction – Live Long, Live Well?

Over the last two centuries, life expectancy in developed countries has been increasing at a rate of approximately 3 months per year, with no plateau in sight. By 2050, the average life expectancy is forecast to be 96.4 years.<sup>1,2</sup> However, this increase in longevity or “lifespan”—which is generally credited to advances in hygiene and sanitation, infection control, improved medications, nutrition, and education—does not necessarily correlate with a person’s ability to live a healthier life, or “healthspan.” For example, between 2000 and 2012, global life expectancy increased by 4.1 years, but the corresponding increase in healthy years was only 2.7.<sup>3</sup>

Many theories about aging have emerged and faded, but—despite tremendous advances in technology and our understanding of physiology, genetics, and biochemistry—the true nature of the aging process remains uncertain.<sup>4</sup> Aging is inevitable, part of everyone’s life. However, while most agree that getting older does beat the proverbial alternative, it is now understood that although some aging processes are natural, many phenomena previously thought to be part of natural aging actually represent signs of pathology. Two major conclusions drawn from the National Institute of Aging’s landmark effort, the Baltimore Longitudinal Study of Aging (BLSA), were that 1) “normal” aging can be distinguished from disease, and that 2) no single, chronological timetable of human aging exists—we all age differently according to our genetics, lifestyle, and individual disease processes.<sup>5</sup>

The first conclusion from the BLSA study indicates that aging involves processes that are completely natural. Some include harmless cosmetic changes, but others may comprise more daunting transformations, such as decreased brain volume and lung capacity, immunosenescence, atherosclerosis, and a reduced ability to maintain nutritional balance. This may seem discouraging, but does it necessarily follow that we should simply resign to die at 75, as suggested by Ezekiel Emanuel, one of the architects of Obamacare?<sup>6</sup> Perhaps not. We now understand that many of the changes commonly attributed to aging, such as altered personality or increased risk for cardiovascular or cardiometabolic disease, are signs of pathology and are, in many cases, preventable with timely identification and appropriately tailored intervention.

The first conclusion reached by the BLSA investigators was crucial to our understanding of aging and our ability to differentiate physiological aging from pathological

processes. The second conclusion, however, carries a potentially even greater promise for our future pursuit of the “healthy aging phenotype.”<sup>1</sup> It is now understood that aging is a vastly complex and multifactorial process that affects everyone differently. While an individual’s genotype is thought to explain roughly 25% of the variation in life expectancy, other factors such as environment and lifestyle (e.g., pollution, stress, infections, access to health care, financial security) provide the remaining balance. Furthermore, the aging process occurs at varying rates in different tissues and appears to also include a significant stochastic element.<sup>1,7-9</sup> Given the complexity and diverse nature of aging, a complete understanding of this intricate network of mechanisms can only be achieved through a melding of insights provided by comprehensive and individualized exploration at the cardiovascular, metabolic, hormonal, and neuroendocrine levels.



## Healthy Aging – One Size Does Not Fit All

The last two decades have seen an increased emphasis on system-level, integrated science as clinical researchers have recognized that the characterization of single genes and proteins has provided only limited insight and benefits toward early diagnoses, improved subtyping and prognoses, and treatment of diseases. This integrative approach is critical for our ability to elucidate the network of structural, regulatory, and dynamic interactions, thereby providing a comprehensive understanding of the physiology and pathophysiology that ultimately leads to effective intervention strategies. In particular, laboratory tests have been used to stratify risk and guide medical decision support for decades. In recent years, however, novel biomarkers and comprehensive biomarker panels provided by some clinical laboratories have brought these tests into the health care delivery process and are changing the face of medicine. Comprehensive testing provides insight into the individual patient's pathophysiology, allowing clinicians and other health care professionals to tailor a specific lifestyle intervention that includes nutrition, exercise, dietary supplementation, and medication, as necessary.

Consider cardiovascular (CV) and cardiometabolic (CM) diseases, for example. Both are complex and multifactorial, and represent the main age-related diseases.<sup>10</sup> Thus, controlling risk factors for these conditions will help to reduce their incidence, leading to a healthy lifespan. In CV disease (CVD), it is crucial to appreciate that lipids and lipoproteins represent only the tip of the iceberg underlying the disease process. Factors such as inflammation, oxidation, myocardial stress, genetics, and many others must be considered to gain a full understanding of the pathophysiology involved. In CM disease, traditional risk stratification metrics, such as glycemic control determined by blood glucose measurements, are the last to become abnormal. Advanced markers that detect insulin resistance and pancreatic beta-cell dysfunction provide much earlier warning signs of pathology, allowing clinicians to identify and engage at-risk patients at a time when intervention is most effective.<sup>10</sup> The following sections describe four panels of markers used in comprehensive risk assessment that provide a methodology for personalized lifestyle intervention.

### Markers of Cardiovascular Health

Age is a key risk factor for coronary artery disease (CAD). Age-related changes in the CV system can lead to increased risk of CVD, such as atherosclerosis, hypertension, myocardial infarction, and stroke.<sup>11</sup> Aging men and women experience hormonal changes, inducing weight gain and unfavorable lipid profiles, coupled with increasing risk for CVD.<sup>12,13</sup> Conversely, favorable lipid metabolism and lower CVD prevalence are associated with longevity and healthy aging. Although traditional lipid concentrations, i.e., total cholesterol, and low- and

high-density lipoprotein cholesterol (LDL-C and HDL-C) are often used as surrogates for lipoprotein particle number, comprehensive testing of lipids and lipoproteins provides a more accurate assessment of CVD risk.<sup>14,15</sup> In addition, comprehensive biomarkers are associated with longevity and cognitive function, and some have been proposed as biomarkers for the rate of biological aging.<sup>16-19</sup> For example, centenarians and their offspring have significantly larger particles of LDL and HDL, which are associated with lower prevalence of hypertension, CVD, and metabolic syndrome.<sup>16-18</sup> In the elderly, cognitive decline is associated with lower plasma HDL and apolipoprotein A-I (apoA-I) concentrations, and increased levels of triglycerides and apolipoprotein B (apoB).<sup>16-18</sup> Thus, the preservation of CV health, through maintaining optimal levels of lipids and lipoproteins, is essential for augmenting both lifespan and healthspan.

### Cardiometabolic Markers

Insulin resistance and diabetes are widely recognized risk factors for CVD. Adults with diabetes are 2- to 4-fold more likely to have heart disease or stroke than those without diabetes, and at least 65% of individuals with diabetes die from CVD.<sup>20</sup> In addition to predicting CVD and mortality, insulin resistance amplifies chronic inflammation—a major risk factor for aging—and is an important effector of morbidity during the aging process, substantially increasing the risk of cognitive impairment, neurodegenerative disease, and physical disability.<sup>21-23</sup> Early identification and treatment of CM disorders are thus vital to healthy aging. In addition to traditional markers such as hemoglobin A1c (HbA1c) and insulin, newer markers such as adiponectin, leptin, and alpha-hydroxybutyrate (β-HB), have been implicated as risk factors for bone loss, cognitive decline, and neurodegenerative disorders, as well as increased mortality in older individuals.<sup>24-31</sup>

### Markers of Inflammation

Although acute inflammation provides a protective physiological response to stimuli such as traumatic injury and infection, chronic inflammation can cause substantial tissue damage and is widely accepted as a risk factor for aging. Low-grade, systemic inflammation is integrally involved in the pathogenesis of major age-related diseases such as CVD, diabetes, cancer, and Alzheimer's disease, and contributes to many conditions that reduce quality of life as we age, including sarcopenia, degenerative arthritis, osteoporosis, and frailty.<sup>32-34</sup> Inflammation may also induce oxidative stress, which augments tissue damage and further amplifies the inflammatory response—creating a vicious feedback loop that greatly increases the risk of poor health outcomes during the aging process.<sup>35</sup> Circulating markers of inflammation, such as high-sensitivity C-reactive protein (hs-CRP) and fibrinogen, are strong predictors of age-related morbidity and mortality<sup>33,36-38</sup>; moreover, they may help identify individuals with early-stage vascular inflammation and/or subclinical CVD, which is associated with premature aging.<sup>39</sup>





## Hormone Markers

The hormones of the hypothalamus, pituitary gland, and gonads cooperatively regulate a range of important physiological functions, including development, reproduction, and aging. Measurement of circulating hormone levels can aid in the assessment and diagnosis of a variety of conditions, as proper hormonal balance and homeostasis is vital for overall health and wellbeing. Hormone deficiencies are also integrally related to the general health decline that often accompanies normal aging. For example, loss of testosterone and estrogen in older men and women is associated with signs and symptoms such as physical weakness, decreased muscle mass and bone mineral density, obesity, loss of libido, and depression.<sup>40,41</sup> Men and women with low testosterone levels are also at increased risk for CV events, CV-related mortality, and all-cause mortality.<sup>42-45</sup> Several reports have provided provocative evidence that decreased physical activity and increased obesity can cause declining testosterone levels in middle-aged and older men. However, it remains unclear whether healthy lifestyle behaviors and maintenance of optimal weight are sufficient for the preservation of testosterone levels during aging and improved health outcomes.<sup>46-48</sup> Other aging-related hormone markers include dehydroepiandrosterone sulfate (DHEA-S), the common precursor for most steroid hormones, which has been shown to have anti-inflammatory and anti-oxidative activity, and is thought to have regenerative effects. In particular, DHEA-S deficiency has been associated with prolonged psychosocial stress, providing a possible mechanistic link between chronic stress and accelerated aging.<sup>49</sup> In general, the identification and treatment of hormone imbalances can help maintain good health, independence, and physical and emotional wellbeing during the aging process.

## The Future – Well Beyond Medicine

Despite the lack of a single mechanism that underlies healthy aging, the increase in human lifespan and, to a lesser degree, healthspan demonstrates that the process has been, and can continue to be, affected to some degree. Even though some common pathways in the aging process have been identified, pursuit of the “healthy aging phenotype” requires a multifactorial and individualized approach that takes advantage of system-level, personalized insights provided by technologies such as comprehensive biomarker testing. We have come to understand that population-based approaches to health care, resulting in guidelines and suggestions such as the Polypill (comprising a statin, three antihypertensives, an aspirin, and folic acid), aimed to reduce CVD by over 80%,<sup>50</sup> do not constitute long-term, strategic solutions. Rather, they represent short-term, reactive measures intended to counteract the multitude of unhealthy lifestyle choices we make that put us at risk. It is crucial to leverage tools that can identify the multifactorial nature of CVD risk factors and stratify at-risk individuals, and then to intervene appropriately with treatments tailored to each specific individual and the etiology of their particular pathology. These approaches have been shown to result not only in improved patient health, but also reduced health care expenses.<sup>51</sup> Therefore, an integrative, preventive, and tailored approach that combines lifestyle and appropriate pharmaceutical intervention cannot remain the exception in our health care, but rather must become a rule and integral component of clinical practice and patient care.

*“The doctor of the future will give no medicine but will interest his patients in the care of the human frame, in diet and in the cause and prevention of disease.”*  
~Thomas Edison

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