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Review

Biological Age Predictors

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ABSTRACT

The search for reliable indicators of biological age, rather than chronological age, has been ongoing for over three decades, and until recently, largely without success. Advances in the fields of molecular biology have increased the variety of potential candidate biomarkers that may be considered as biological age predictors. In this review, we summarize current state-of-the-art findings considering six potential types of biological age predictors: epigenetic clocks, telomere length, transcriptomic predictors, proteomic predictors, metabolomics-based predictors, and composite biomarker predictors. Promising developments consider multiple combinations of these various types of predictors, which may shed light on the aging process and provide further understanding of what contributes to healthy aging. Thus far, the most promising, new biological age predictor is the epigenetic clock; however its true value as a biomarker of aging requires longitudinal confirmation.

Contents

1. Introduction

Chronological age is a major risk factor for functional impairments, chronic diseases and mortality. However, there is still great heterogeneity in the health outcomes of older individuals (Lowsky et al., 2014). Some individuals appear frail and require assistance in daily routines

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already in their 70′s whereas others remain independent of assistance and seem to escape major physiological deterioration until very extreme ages. In keeping with the unprecedented growth rate of the world's aging population, there is a clear need for a better understanding of the biological aging process and the determinants of healthy aging. Towards this aim, a quest for (biological) markers that track the state of biophysiological aging and ideally lend insights to the underlying mechanisms has been embarked upon.

During the past decades, extensive effort has been made to identify such aging biomarkers that, according to the stage-setting definition (Baker and Sprott, 1988), are "biological parameters of an organism that either alone or in some multivariate composite will, in the absence of disease, better predict functional capability at some late age, than will chronological age". Later on, the American Federation for Aging Research (AFAR) formulated the criteria for aging biomarkers as follows (Johnson, 2006; Butler et al., 2004):

1. It must predict the rate of aging. In other words, it would tell exactly where a person is in their total life span. It must be a better predictor of life span than chronological age.
2. It must monitor a basic process that underlies the aging process, not the effects of disease.
3. It must be able to be tested repeatedly without harming the person. For example, a blood test or an imaging technique.
4. It must be something that works in humans and in laboratory animals, such as mice. This is so that it can be tested in lab animals before being validated in humans.

However, to date, no such marker or marker combination has emerged. Moreover, the existence of such markers has been questioned, because the effects of many chronic diseases are inseparable from normal aging. The rate of biological aging can also vary across different tissues, and hence it may not be feasible to assume a measurable overall rate. On the other hand, as consensus around the definition is missing, the term "aging biomarker" has been widely used in the literature as reviewed in (Lara et al., 2015; Johnson, 2006; Engelfriet et al., 2013).

Recently, several new biomarkers for biological aging have come into play. They can be separated into molecular- (based on DNA, RNA etc.) or phenotypic biomarkers of aging (clinical measures such as blood pressure, grip strength, lipids etc.), although we include both types. The focus of this review is on novel biological age predictors, and we define them as markers that predict chronological age, or at least can separate "young" from "old". They should also be associated with a normal aging phenotype or a non-communicable age-related disease independent of chronological age in humans (Fig. 1). A list of the final biological age predictors discussed in the paper can be found in Table 1.

2. Search Strategy and Selection Criteria

PubMed was used as the search engine where Medical Subject Headings (MeSH) terms "Aging" and "Humans" and the specific term for each of the six marker categories: 1) Epigenetic clock, 2) Telomere length, 3) Transcriptomics, 4) Proteomics, 5) Metabolomics, and 6) Multi-biomarker, were combined. Cited papers in the selected publications and papers that referenced the selected publications were also considered. We also searched in bioRxiv using a combination of the following search terms: "aging", "biomarker", "humans" and each of the six marker categories described above. The searches were performed between 22nd of November 2016 and 16th of January 2017.

We limited the discussion to those predictors that have been trained/identified in a discovery population of human adults, and then validated in a separate cohort. Only scores derived from multiple measurements, such as different probe signals, were considered (except for telomere length due to its classical role as benchmark biomarker), and studies published in English from 2010 and onwards were included.

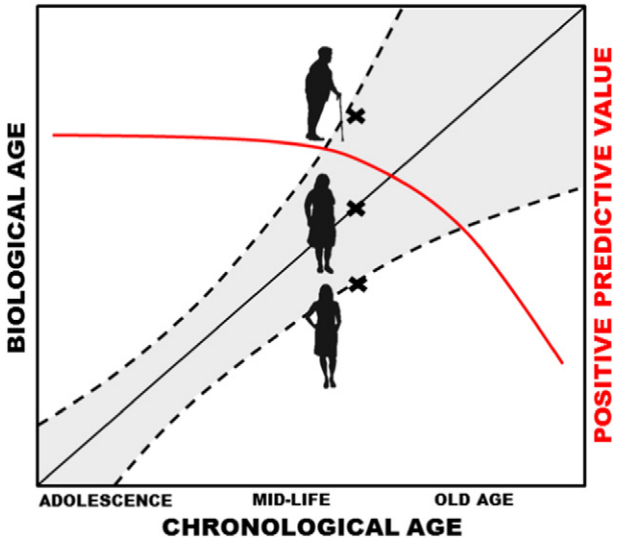

Fig. 1. The concept of biological age predictors. A biological age predictor could be defined as a biomarker correlated with chronological age (black line), which brings additive information in the risk assessments for age-related conditions on top of chronological age. Hence, adult individuals of the same chronological age could possess different risks for age-associated diseases as judged from their biological ages (x's in figure). Usually, the positive predictive value (red line) of a biological age predictor decreases from mid-life and onwards due to the increased biological heterogeneity at old age (confidence interval described by dashed lines increases at old age).

2.1. Epigenetic Clock

A number of recent studies have identified a measure of DNA methylation age (DNAmAge), also referred to as the epigenetic clock, as a viable biological age predictor. Two of these clock measures, (Horvath, 2013) and (Hannum et al., 2013) calculators, are currently perhaps the most robust predictors of chronological age. Both of them show high age correlations ($r = 0.96$ for Horvath and $r = 0.91$ for Hannum) and small, mean deviations from calendar age (3.6 and 4.9 years, respectively) in their corresponding validation cohorts (Hannum et al., 2013; Horvath, 2013). Both algorithms have been developed in large samples ($n = 8000$ for Horvath and $n = 656$ for Hannum) covering the entire adult life span and different ethnic populations. The Horvath clock is a multi-tissue predictor based on methylation levels of 353 CpG sites on the Illumina 27 k array, whereas the Hannum clock uses only 71 CpG sites from the Illumina 450 k array and performs best using whole blood samples. Selection of the CpG sites for both predictors was done using a similar penalized regression model, yet they only have six CpG sites in common. Nevertheless, the correlations between the clocks appear to vary from fairly strong ($r = 0.76$) (Chen et al., 2016) to moderate ($r = 0.37$) (Belsky et al., 2016) in independent studies.

2.1.1. DNAmAge and Mortality

The most striking feature of the Horvath and Hannum clocks is their ability to predict all-cause mortality independent of classic risk factors. A recent meta-analysis in 13 different cohorts with a total sample size of 13,089 demonstrated that the epigenetic clock was able to predict all-cause mortality independent of several risk factors such as age, body mass index (BMI), education, smoking, physical activity, alcohol use, smoking and certain comorbidities (Chen et al., 2016). When the authors divided the samples into subgroups by race, sex, follow-up time, BMI, smoking status, physical activity and given comorbidities they could, with some exceptions, observe largely similar mortality associations across subgroups (Chen et al., 2016). Furthermore, they showed that a weighted average of the Hannum clock based on distinct