



REVIEW

# Molecular and phenotypic biomarkers of aging [version 1; referees: 3 approved]

Xian Xia<sup>1</sup>, Weiyang Chen<sup>2</sup>, Joseph McDermott<sup>1</sup>, Jing-Dong Jackie Han <sup>1</sup>

<sup>1</sup>Key Laboratory of Computational Biology, CAS Center for Excellence in Molecular Cell Science, Collaborative Innovation Center for Genetics and Developmental Biology, Chinese Academy of Sciences-Max Planck Partner Institute for Computational Biology, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, Shanghai, China

<sup>2</sup>School of Information, Qilu University of Technology, Jinan, China

**v1** First published: 09 Jun 2017, 6(F1000 Faculty Rev):860 (doi: 10.12688/f1000research.10692.1)


Latest published: 09 Jun 2017, 6(F1000 Faculty Rev):860 (doi: 10.12688/f1000research.10692.1)

**Abstract**

Individuals of the same age may not age at the same rate. Quantitative biomarkers of aging are valuable tools to measure physiological age, assess the extent of 'healthy aging', and potentially predict health span and life span for an individual. Given the complex nature of the aging process, the biomarkers of aging are multilayered and multifaceted. Here, we review the phenotypic and molecular biomarkers of aging. Identifying and using biomarkers of aging to improve human health, prevent age-associated diseases, and extend healthy life span are now facilitated by the fast-growing capacity of multilevel cross-sectional and longitudinal data acquisition, storage, and analysis, particularly for data related to general human populations. Combined with artificial intelligence and machine learning techniques, reliable panels of biomarkers of aging will have tremendous potential to improve human health in aging societies.

**Open Peer Review**

Referee Status: 

	Invited Referees		
	1	2	3
<b>version 1</b> published 09 Jun 2017			

F1000 Faculty Reviews are commissioned from members of the prestigious F1000 Faculty. In order to make these reviews as comprehensive and accessible as possible, peer review takes place before publication; the referees are listed below, but their reports are not formally published.

- 1 **Eileen Crimmins** , University of Southern California, USA
- 2 **Alan Cohen** , University of Sherbrooke, Canada
- 3 **Kristina Endres** , University Medical Center of the Johannes Gutenberg University Mainz, Germany

**Discuss this article**

Comments (0)

**Corresponding author:** Jing-Dong Jackie Han ([jdhan@picb.ac.cn](mailto:jdhan@picb.ac.cn))

**Competing interests:** The authors declare that they have no competing interests.

**How to cite this article:** Xia X, Chen W, McDermott J and Han JDJ. **Molecular and phenotypic biomarkers of aging [version 1; referees: 3 approved]** *F1000Research* 2017, **6**(F1000 Faculty Rev):860 (doi: [10.12688/f1000research.10692.1](https://doi.org/10.12688/f1000research.10692.1))

**Copyright:** © 2017 Xia X *et al.* This is an open access article distributed under the terms of the [Creative Commons Attribution Licence](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

**Grant information:** This work was supported by grants from the China Ministry of Science and Technology (2015CB964803 and 2016YFE0108700) and the National Natural Science Foundation of China (91329302, 31210103916, and 91519330) and the Chinese Academy of Sciences XDB19020301 and XDA01010303 to J-DJH.

*The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.*

**First published:** 09 Jun 2017, **6**(F1000 Faculty Rev):860 (doi: [10.12688/f1000research.10692.1](https://doi.org/10.12688/f1000research.10692.1))

## Introduction: Why do we need biomarkers of aging?

Aging is the time-dependent physiological functional decline that affects most living organisms, which is underpinned by alterations within molecular pathways, and is also the most profound risk factor for many non-communicable diseases. To identify biomarkers of aging would, on one hand, facilitate differentiation of people who are of the same chronological age yet have variant aging rates. Quantitative biomarkers of aging could also define a panel of measurements for 'healthy aging' and, even further, predict life span. On the other hand, biomarkers of aging could also assist researchers to narrow their research scope to a specific biological facet in their attempts to explain the biological process behind aging or aging-related diseases. Here, we review the phenotypic and molecular biomarkers of aging. Phenotypic biomarkers can be non-invasive, panoramic, and easy to obtain, whereas molecular biomarkers can reflect some of the molecular mechanisms underlying age status. This review is centered on humans (with mouse and nematode in some rare cases).

## Molecular biomarkers of aging

This section is inspired by two high-impact reviews on the hallmarks of aging<sup>1,2</sup>. Following the framework of these reviews, we focus on developments since 2013. The American Federation for Aging Research (AFAR) has proposed the following criteria for a biomarker of aging: (1) it must predict the rate of aging; (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; and (4) it must be something that works in humans and in laboratory animals.

Biomarkers fulfilling all of the criteria proposed by the AFAR are unlikely to exist<sup>3</sup>, so in the molecular part of this review we follow the first two criteria: a biomarker should predict the rate of aging, and it must monitor a basic process that underlies the aging process. For the first criterion, we required the biomarker to be correlated with aging; for the second criterion, we have organized the first part of this review according to the molecular pathways underlying aging.

## DNA and chromosomes

**Telomeres.** Telomeres are ribonucleoprotein complexes at the end of chromosomes and become shorter after each replication, as telomerase, the enzyme responsible for its replication, is not regularly expressed in somatic cells<sup>4</sup>. The length of telomeres in leukocytes has been associated with aging and life span<sup>5</sup> as well as age-related diseases, such as cardiovascular diseases<sup>6,7</sup>, cancer<sup>8</sup>, and neurological disorders<sup>9</sup>.

**DNA repair.** The link between DNA damage and repair has been implicated in aging by the accumulation of senescent cells<sup>10</sup> or genomic rearrangements<sup>11</sup>. More recently, this link was directly demonstrated, and controlled induction of DNA double-strand breaks in mouse liver inducing aging pathologies and gene expression was shown<sup>12</sup>. Immunohistochemistry of  $\gamma$ -H2A.X is an established quantitative biomarker of aging because H2A.X is a variant of the H2A protein family, and phosphorylated H2A.X,  $\gamma$ -H2A.X, is an initial and essential component of DNA damage foci and

therefore a reliable marker of the extent of DNA damage<sup>13–15</sup>. Serum markers of DNA damage, including CRAMP, EF-1a, stathmin, N-acetyl-glucosaminidase, and chitinase, have also been established<sup>16</sup>. Of note, the dermal fibroblasts from centenarian donors were shown to be less sensitive to H<sub>2</sub>O<sub>2</sub>-induced DNA damage than fibroblasts from young and old donors<sup>17</sup>. Such *ex vivo* experiments could also be a potential biomarker of aging.

**Epigenetic modifications.** Age-related changes in DNA methylation patterns, notably as measured by the epigenetic clock, are among the best-studied aging biomarkers<sup>18–20</sup>. Analysis of methylation profiles in the blood found that only three CpG sites could predict age with a mean absolute deviation from chronological age of less than 5 years<sup>21</sup>. The association between age and DNA methylation can be extended to age-associated diseases, such as diabetes<sup>22</sup>. For a full review of the epigenetic regulation of aging, see Sen *et al.*<sup>23</sup>.

## RNA and transcriptome

**Transcriptome profiles.** With rapid progress in single-cell RNA sequencing (RNA-seq) technology, it has begun to be applied to the study of biomarkers of aging. Lu *et al.* have recently shown that cell-to-cell expression variation, as measured by single-cell RNA-seq of high-dimensional flow cytometry sorted T cells, is associated with aging and disease susceptibility<sup>24</sup>.

A recent study used whole-blood gene expression profiles from 14,983 individuals to identify 1,497 genes with age-dependent differential expression and then used them to calculate the 'transcriptomic age' of an individual, suggesting that transcriptome signatures can be used to measure aging<sup>25</sup>.

**Non-coding RNAs.** MicroRNAs (miRNAs) are a class of small (21- to 23-nucleotide) non-coding RNAs that, through base-pairing mechanisms, regulate a broad range of biological processes, including metabolism<sup>26</sup> and aging<sup>27</sup>. Among them, circulating miRNAs can be stable in plasma by residing in exosomes or binding to protein or lipoprotein factors, thus making them easy-to-access biomarkers. miR-34a was the first observed circulating miRNA with an altered expression pattern during mouse aging<sup>28</sup>. Its expression is found to correlate with age-related hearing loss in mice and humans<sup>29</sup>. miR-21 was defined as an inflammatory biomarker in a study of 365 miRNAs in the plasma of healthy and old humans<sup>30</sup>. miR-151a-3p, miR-181a-5p, and miR-1248 are reported to be significantly decreased with age in humans, in which all three miRNAs also show indications of associations with inflammation<sup>31</sup>. miR-126-3p has been found to be positively correlated with age in 136 healthy subjects from 20 to 90 years of age<sup>32</sup>. Through expression of GFP driven by miRNA promoters, Pincus *et al.* found that levels of *mir-71*, *mir-246*, and *mir-239* in early adulthood vary across individuals and are predictive of life span<sup>33</sup>. A recent review<sup>27</sup> summarized the associations of other types of circulating non-coding small RNAs, such as tRNA and YRNA.

Long non-coding RNAs (lncRNAs) are a heterogeneous class of non-coding RNAs which are defined as transcripts longer than 200 nucleotides and devoid of evident open reading frames<sup>34</sup>. Two recent reviews summarize the role of lncRNAs in aging<sup>35,36</sup>. The

diverse functional mechanisms of lncRNA are beyond the scope of this review, and readers may consult a recent review on this topic<sup>37</sup>; here, we list lncRNAs that function in aging. The lncRNA MIR31HG was identified to be upregulated in oncogene-induced senescence and required for polycomb group-mediated repression of the INK4A locus<sup>38</sup>. Downregulation of lncRNA AK156230 occurs in replicative senescence and its knockdown in mouse embryonic fibroblasts induces senescence through dysregulation of autophagy and cell cycle pathways, as shown by expression profiles<sup>39</sup>. Meg3 is upregulated during cardiovascular aging as well as in senescent human umbilical venous endothelial cells<sup>40</sup>. As most of the lncRNAs studies have been anecdotal, high-throughput lncRNA studies, such as CRISPR-Cas9 screen of functional lncRNAs<sup>41</sup>, will be a useful future step toward understanding lncRNA functions in the aging process.

### Metabolism

That dietary restriction is the most conserved means to extend life span and health span from yeast to mammals<sup>42</sup> points to a pivotal role of metabolism in aging regulation and to the potential for metabolic factors to be biomarkers.

**Nutrient sensing.** The insulin/insulin-like growth factor 1 (IGF-1) signaling (IIS) pathway, which participates in glucose sensing, is the earliest discovered and the most well-known pathway to antagonize longevity. Paradoxically, IGF-1 declines in wild-type mice or mouse models of premature aging whereas attenuating IIS activity extends life span<sup>43</sup>. Such observations led to the potential inclusion of IIS pathway members, such as growth hormone and IGF-1, as biomarkers of aging<sup>44,45</sup>.

The mechanistic target of rapamycin (mTOR) protein senses high amino acid concentrations. Inhibition of mTOR can extend life span<sup>46</sup>. Unlike the IIS pathway, mTOR activity increases with age in the ovarian surface epithelium of aged human and mouse ovaries, which contributes to pathological changes<sup>47</sup>. Phosphorylated S6 ribosomal protein (p-S6RP, or pS6) is a downstream target and also a known marker of active mTOR signaling<sup>47,48</sup>, which is a potential biomarker of aging as indicated in the research of aged ovaries<sup>47</sup>.

In contrast to IIS and mTOR function, 5'-adenosine monophosphate (AMP)-activated protein kinase (AMPK) and sirtuins sense nutrient scarcity instead of abundance. AMPK detects high AMP levels whereas sirtuins are sensors of high NAD<sup>+</sup> levels, and both mark low-energy states. The upregulation of AMPK activity by metformin, a drug for type II diabetes, could mimic some of the benefits of caloric restriction, and metformin extends life span in male mice<sup>49</sup>. AMPK is upregulated with age in skeletal muscles<sup>50</sup>.

Sirtuins have the ability to directly link cellular metabolic signaling (reflected by NAD<sup>+</sup>) to protein post-translational modifications through a chemical reaction (deacetylation of lysine). During aging, NAD<sup>+</sup> is reduced<sup>51</sup> and sirtuins are downregulated<sup>52,53</sup>. An analysis of primary human dermal fibroblasts found that SIRT1 and SIRT6 are downregulated through passaging<sup>54</sup>. Similarly, levels of SIRT1, SIRT3, and SIRT6 detected by Western blotting showed significant decrease in ovaries of aged mice<sup>55</sup>. In human peripheral blood mononuclear cells, SIRT2 also decreases with age<sup>56</sup>.

**Protein metabolism.** Protein carbamylation is one of the non-enzymatic post-translational modifications which occur throughout the whole life span of an organism, leading to tissue accumulation of carbamylated proteins<sup>57</sup>. It is considered a hallmark of molecular aging and is related to aging-related diseases, such as cardiovascular disease<sup>58</sup>.

Advanced glycation end products (AGEs) are a heterogeneous group of bioactive molecules that are formed by non-enzymatic glycation of proteins, lipids, and nucleic acids<sup>59</sup>. Accumulation of AGEs in aging tissues leads to inflammation<sup>60</sup>, apoptosis<sup>61</sup>, obesity<sup>62</sup>, and other age-related disorders<sup>63</sup>. AGEs can be detected via high-performance liquid chromatography, gas chromatography-mass spectrometry, and immunochemical techniques<sup>64</sup>. N-glycans are a class of glycoproteins with sugar chains bonded to the amide nitrogen of asparagine. The spectrum of N-linked glycans (the N-glycome) can now be investigated because of the development of high-throughput methods. The accumulation of N-linked glycation at Asn297 of the Fc portion of IgG (IgG-G0) can contribute to low-grade pro-inflammatory status in aging<sup>65</sup>.

**Lipid metabolism.** Triglycerides are found to increase monotonously with age and thus could be a biomarker of aging<sup>66</sup>. Studies of serum samples by shotgun lipidomics found that phospho/sphingolipids are putative markers, and biological modulators, of healthy aging<sup>67</sup>. However, the design of these studies is questionable in that they have a group of elderly individuals as a 'not healthy aging control' and compare them with the 'successful aging' centenarian group<sup>67,68</sup>, but the two groups are obviously of very different ages. Therefore, it is not clear whether it was the age difference or the success of healthy aging that contributed to the differences in lipidomics.

### Oxidative stress and mitochondria

Biomarkers of oxidative stress have long been regarded as a class of aging biomarkers. The products of oxidative damage to proteins include o-tyrosine, 3-chlorotyrosine, and 3-nitrotyrosine. 8-iso prostaglandin F<sub>2α</sub> is a biomarker for phospholipid damage. 8-hydroxy-2'-deoxyguanosine and 8-hydroxyguanosine are produced by the oxidative damage of nucleic acids<sup>69</sup>. The concentration of these biomarkers in body fluids can be detected via high-performance liquid chromatography and mass spectrometry. Shen *et al.* engineered a circularly permuted yellow fluorescent protein (cpYFP) expressed in *Caenorhabditis elegans* mitochondrial matrix as a sensor of oxidative stress and metabolic changes; the authors found that adult day 3 mitochondrial cpYFP flash frequency is a good predictor of *C. elegans* life span under different genetic, environmental, and stochastic conditions<sup>70</sup>.

Although free radicals, the source of oxidative stress, are mainly produced in mitochondria, dysfunctional mitochondria can contribute to aging independently of reactive oxygen species. To measure mitochondria function, blood- and-muscle based respirometric profiling strategies are available, and the association of this potential reporter with bioenergetic capacity of other tissues<sup>71</sup> or phenotypes, such as gait speed<sup>72</sup>, has been investigated. Extracellular mitochondria components can function as damage-associated molecular pattern molecules (DAMPs) (see also "Inflammation and

intercellular communication”) and these induce neuroinflammation when injected in mouse hippocampus<sup>73</sup>.

### Cell senescence

In mitotic tissues, the gradual accumulation of senescent cells is thought to be one of the causal factors of aging<sup>74–76</sup>. Thus, the biomarkers of cell senescence can also be used as markers. Such biomarkers have been summarized in recent reviews<sup>77,78</sup>. The most widely used marker is senescence-associated  $\beta$ -galactosidase (SA $\beta$ -gal)<sup>79</sup> and p16<sup>INK4A</sup><sup>80,81</sup>. SA $\beta$ -gal reflects increased lysosomal mass<sup>82</sup> but can yield false positives because of its low specificity<sup>83</sup>. SA $\beta$ -gal is a cell damage marker, and p16<sup>INK4A</sup> is required to induce, and is indicative of, permanent cell cycle arrest<sup>81</sup>.

Other senescent cell markers include activated and persistent DNA-damage response (see “DNA repair”), telomere shortening and dysfunction (see “Telomere”), and senescence-associated secretory phenotype (SASP) (see “Inflammation and intercellular communication”).

### Inflammation and intercellular communication

SASP is a consequence of cell senescence and may occur in cells that, though undergoing cell cycle arrest, are still metabolically active and secrete proteins. SASP functions in an autocrine/paracrine manner<sup>84,85</sup>. The major components of SASP factors are soluble signaling factors, including interleukins, chemokines, and growth factors. Proteins that are associated with the SASP, such as interleukin-6, tumor necrosis factor- $\alpha$ , monocyte chemoattractant protein-1, matrix metalloproteinases, and IGF binding proteins, increase in multiple tissues with chronological aging and occur in conjunction with sterile inflammation<sup>86</sup>. Comprehensive catalogs of SASP also include secreted proteases and secreted insoluble proteins/extracellular matrix components and are summarized by Coppé *et al.*<sup>87</sup> and the Reactome database (<http://www.reactome.org/content/detail/R-HSA-2559582>).

The DAMPs, such as heat shock proteins, histones, high-mobility group box 1, and S100, compose a class of molecules released after injury or cellular death<sup>88</sup> and mediate immune response. The association between DAMPs and other hallmarks of aging has been reviewed by Huang *et al.*<sup>89</sup>.

### Phenotypic biomarkers of aging

Still following the criteria proposed by the AFAR<sup>3</sup>, here we categorize the phenotypic biomarkers of aging. It is difficult for phenotypic biomarkers to monitor a basic molecular process that underlies the aging process, so we follow three standards: a biomarker should predict rate of aging, it must be able to be tested repeatedly without harming the person, and it monitors one or more physiological processes.

Physical function and anthropometry are the most practical measurements among phenotypic biomarkers of aging. In this regard, walking speed, chair stand, standing balance, grip strength, body mass index, waist circumference, and muscle mass are well known<sup>90</sup>. These physical functional measurements, though simple, can actually perform better than DNA methylation in terms of relationship to health status in demographic research<sup>91</sup>.

Quantitative phenotypes of external human features also show significant relationships with aging<sup>92,93</sup>. Quantified facial features based on three-dimensional (3D) facial images, such as mouth width, nose width, and eye corner droop, are highly associated with age. In fact, 3D facial images can be used to quantify the biological age of an individual<sup>92</sup>.

### Integration of aging biomarkers

Biomarkers of aging can be used to predict the physiological age, which reflects their state of health, via statistics and machine learning algorithms. A single class of biomarkers, which is intrinsically a matrix of features, can be used in the prediction. DNA methylation was used to predict age with an error of about 3.6 years using 8,000 samples<sup>94</sup>. 3D facial images have also been used to predict age with a mean deviation of 6 years<sup>92</sup>.

Integration of multiple biomarkers can be even more powerful. The Dunedin Study<sup>91</sup> has focused on middle-aged people and used different measurements (telomere lengths, epigenetic clocks, and clinical biomarker composites) and compared their performance in predicting health status, as measured by physical functionality, cognitive decline, and subjective signs of aging. The three types of measurements in this study do not correlate with each other, suggesting that there is no single index of biological age. Therefore, another approach is to use statistic distance,  $D_M$ <sup>95,96</sup>, to assess the degree of deviation of an individual’s biomarker profile from the reference population.  $D_M$  is the Mahalanobis distance<sup>97</sup> of multi-variants (in the simplest case, when all the variants are uncorrelated, this distance is the sum of the absolute values of z-scores), and is proven to be insensitive to biomarker choice across 44 available markers and to be generalizable with multiple marker variants. Recently, a modular ensemble of 21 deep neural networks was used to predict age by using measurements from basic blood tests by training over 60,000 samples, which revealed the five most important blood markers for predicting human chronological age: albumin, glucose, alkaline phosphatase, urea, and erythrocytes<sup>98</sup>.

### Conclusion and outlook

As expected from the complex nature of the aging process, aging biomarkers are multilayered and multifaceted and consist of a dizzying array of parameters, which we further summarized in an even more concise form as a table (Table 1). This, however, does not mean that they are equally useful. We need to point out that not all factors, although they might be involved in the underlying biological process of aging, are proven to be useful in terms of measuring human aging at this point.

Recently, the MARK-AGE project was announced as a large-scale integrated project aimed to find a powerful set of biomarkers for human aging based on over 3,200 subjects<sup>99</sup>. Although more details from this project remain to be seen, the pace of identifying and using biomarkers of aging to improve human health, preventing aging-associated diseases, and extending healthy life span will only be further increased by the myriad of data generated. These include not only data from large human cohort studies but also ordinary people’s genomic, functional genomic, phenotypic, and lifestyle data, which will be facilitated by the ever-growing capacity of data

**Table 1. Biomarkers of aging.** For species source, if there is one in humans, then other model organisms are omitted.

	Biomarker Category	Biomarker Subcategory	Biomarker	Trend with age	Species
Molecular biomarkers	DNA and chromosome	Telomere	Leukocyte telomere length	Decrease	Human
		DNA repair	$\gamma$ -H2A.X immunohistochemistry	Increase	Human
		Epigenetic modification	DNA methylation	Global hypomethylation and local hypermethylation	Human
	RNA and transcriptome	Transcriptome profiles	Heterogeneity of CD38 in CD4 <sup>+</sup> CD27 <sup>+</sup> T cells	Decrease	Human
			Heterogeneity of CD197 in CD4 <sup>+</sup> CD25 <sup>+</sup> T cells	Increase	Human
		Circulating microRNAs (miRNAs)	miR-34a, miR-21, miR-126-3p	Increase	Human
			miR-151a-3p, miR-181a-5p, miR-1248	Decrease	Human
		Long non-coding RNAs	MIR31HG	Increase in cell senescence	Human
			AK156230	Decrease in cell senescence	Mouse
	Meg3		Increase in cell senescence	Human	
	Metabolism	Nutrient sensing	Growth hormone and insulin/insulin-like growth factor 1 (IGF-1)	Decrease	Human
			Mechanistic target of rapamycin (mTOR) and pS6RP	Increase	Human
			NAD <sup>+</sup> , SIRT1, SIRT2, SIRT3, SIRT6	Decrease	Human
		Protein metabolism	Protein carbamylation, such as homocitrulline rate	Increase	Human
			Advanced glycation end products and N-glycans	Increase	Human
		Lipid metabolism	Triglycerides	Increase	Human
	Oxidative stress and mitochondria		o-tyrosine, 3-chlorotyrosine, 3-nitrotyrosine, 8-iso prostaglandin F2 $\alpha$ , 8-hydroxy-2'-deoxyguanosine, 8-hydroxyguanosine	Increase	Human
	Cell senescence		Senescence-associated $\beta$ -galactosidase	Increase in cell senescence	Human
			p16INK4A	Increase in cell senescence	Human
	Inflammation and intercellular communication		Senescence-associated secretory phenotype	Increase	Human
Phenotypic biomarkers	Physical function and anthropometry	Walking speed, chair stand, standing balance, grip strength, muscle mass	Decrease		
		Body mass index, waist circumference	Increase		
	Facial features	Mouth width	Increase		
		Nose width	Increase		
		Mouth-nose distance	Increase		
		Eye corner slope	Decrease		



acquisition, storage, and analysis. It would not be far-fetched for there one day to be an artificial intelligence program capable of precise prognosis of how long a person can live, based on his or her quantitative measurements in a large panel of biomarkers of aging.

### Competing interests

The authors declare that they have no competing interests.

### Grant information

This work was supported by grants from the China Ministry of Science and Technology (2015CB964803 and 2016YFE0108700) and the National Natural Science Foundation of China (91329302, 31210103916, and 91519330) and the Chinese Academy of Sciences XDB19020301 and XDA01010303 to J-DJH.

*The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.*

### References



- López-Otín C, Blasco MA, Partridge L, *et al.*: **The hallmarks of aging.** *Cell*. 2013; **153**(6): 1194–217.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
- Engelkriet PM, Jansen EH, Picavet HS, *et al.*: **Biochemical markers of aging for longitudinal studies in humans.** *Epidemiol Rev*. 2013; **35**(1): 132–51.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
- Johnson TE: **Recent results: biomarkers of aging.** *Exp Gerontol*. 2006; **41**(12): 1243–6.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Aubert G, Lansdorp PM: **Telomeres and aging.** *Physiol Rev*. 2008; **88**(2): 557–79.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Kimura M, Hjelmborg JV, Gardner JP, *et al.*: **Telomere length and mortality: a study of leukocytes in elderly Danish twins.** *Am J Epidemiol*. 2008; **167**(7): 799–806.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
- Rehkopf DH, Needham BL, Lin J, *et al.*: **Leukocyte Telomere Length in Relation to 17 Biomarkers of Cardiovascular Disease Risk: A Cross-Sectional Study of US Adults.** *PLoS Med*. 2016; **13**(11): e1002188.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
- Hammad M, Al Mheid I, Wilmot K, *et al.*: **Telomere Shortening, Regenerative Capacity, and Cardiovascular Outcomes.** *Circ Res*. 2017; **120**(7): 1130–8.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
- Blackburn EH, Epel ES, Lin J: **Human telomere biology: A contributory and interactive factor in aging, disease risks, and protection.** *Science*. 2015; **350**(6265): 1193–8.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- Eitan E, Hutchison ER, Mattson MP: **Telomere shortening in neurological disorders: an abundance of unanswered questions.** *Trends Neurosci*. 2014; **37**(5): 256–63.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Sedelnikova OA, Horikawa I, Zimonjon DB, *et al.*: **Senescing human cells and ageing mice accumulate DNA lesions with unreparable double-strand breaks.** *Nat Cell Biol*. 2004; **6**(2): 168–70.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- Dollé ME, Giese H, Hopkins CL, *et al.*: **Rapid accumulation of genome rearrangements in liver but not in brain of old mice.** *Nat Genet*. 1997; **17**(4): 431–4.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- White RR, Milholland B, de Bruin A, *et al.*: **Controlled induction of DNA double-strand breaks in the mouse liver induces features of tissue ageing.** *Nat Commun*. 2015; **6**: 6790.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
- Wang C, Jurk D, Maddick M, *et al.*: **DNA damage response and cellular senescence in tissues of aging mice.** *Aging Cell*. 2009; **8**(3): 311–23.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Rübe CE, Fricke A, Widmann TA, *et al.*: **Accumulation of DNA damage in hematopoietic stem and progenitor cells during human aging.** *PLoS One*. 2011; **6**(3): e17487.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Kuo LJ, Yang LX: **Gamma-H2AX - a novel biomarker for DNA double-strand breaks.** *In Vivo*. 2008; **22**(3): 305–9.  
[PubMed Abstract](#)
- Song Z, von Figura G, Liu Y, *et al.*: **Lifestyle impacts on the aging-associated expression of biomarkers of DNA damage and telomere dysfunction in human blood.** *Aging Cell*. 2010; **9**(4): 607–15.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Chevanne M, Calchini R, Tombaccini D, *et al.*: **Comparative levels of DNA breaks and sensitivity to oxidative stress in aged and senescent human fibroblasts: a distinctive pattern for centenarians.** *Biogerontology*. 2003; **4**(2): 97–104.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Day K, Waite LL, Thalacker-Mercer A, *et al.*: **Differential DNA methylation with age displays both common and dynamic features across human tissues that are influenced by CpG landscape.** *Genome Biol*. 2013; **14**(9): R102.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Horvath S, Zhang Y, Langfelder P, *et al.*: **Ageing effects on DNA methylation modules in human brain and blood tissue.** *Genome Biol*. 2012; **13**(10): R97.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Horvath S, Gurven M, Levine ME, *et al.*: **An epigenetic clock analysis of race/ethnicity, sex, and coronary heart disease.** *Genome Biol*. 2016; **17**(1): 171.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Weidner CI, Lin Q, Koch CM, *et al.*: **Ageing of blood can be tracked by DNA methylation changes at just three CpG sites.** *Genome Biol*. 2014; **15**(2): R24.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Bacos K, Gillberg L, Volkov P, *et al.*: **Blood-based biomarkers of age-associated epigenetic changes in human islets associate with insulin secretion and diabetes.** *Nat Commun*. 2016; **7**: 11089.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
- Sen P, Shah PP, Nativio R, *et al.*: **Epigenetic Mechanisms of Longevity and Aging.** *Cell*. 2016; **166**(4): 822–39.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- Lu Y, Biancotto A, Cheung F, *et al.*: **Systematic Analysis of Cell-to-Cell Expression Variation of T Lymphocytes in a Human Cohort Identifies Aging and Genetic Associations.** *Immunity*. 2016; **45**(5): 1162–75.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- Peters MJ, Joehanes R, Pilling LC, *et al.*: **The transcriptional landscape of age in human peripheral blood.** *Nat Commun*. 2015; **6**: 8570.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
- Dumortier O, Hinault C, Van Obberghen E: **MicroRNAs and metabolism crosstalk in energy homeostasis.** *Cell Metab*. 2013; **18**(3): 312–24.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Dhahbi JM: **Circulating small noncoding RNAs as biomarkers of aging.** *Ageing Res Rev*. 2014; **17**: 86–98.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Li X, Khanna A, Li N, *et al.*: **Circulatory miR34a as an RNA-based, noninvasive biomarker for brain aging.** *Aging (Albany NY)*. 2011; **3**(10): 985–1002.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Pang X, Xiong H, Yang H, *et al.*: **Circulating miR-34a levels correlate with age-related hearing loss in mice and humans.** *Exp Gerontol*. 2016; **76**: 58–67.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- Olivieri F, Spazzafumo L, Santini G, *et al.*: **Age-related differences in the expression of circulating microRNAs: miR-21 as a new circulating marker of inflammation.** *Mech Ageing Dev*. 2012; **133**(11–12): 675–85.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Noren Hooten N, Fitzpatrick M, Wood WH 3rd, *et al.*: **Age-related changes in microRNA levels in serum.** *Aging (Albany NY)*. 2013; **5**(10): 725–40.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Olivieri F, Bonafè M, Spazzafumo L, *et al.*: **Age- and glycemia-related miR-126-3p levels in plasma and endothelial cells.** *Aging (Albany NY)*. 2014; **6**(9): 771–87.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Pincus Z, Smith-Vikos T, Slack FJ: **MicroRNA predictors of longevity in**

- Caenorhabditis elegans.** *PLoS Genet.* 2011; 7(9): e1002306.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
34. Fatica A, Bozzoni I: **Long non-coding RNAs: new players in cell differentiation and development.** *Nat Rev Genet.* 2014; 15(1): 7–21.  
[PubMed Abstract](#) | [Publisher Full Text](#)
35. Grammatikakis I, Panda AC, Abdelmohsen K, *et al.*: **Long noncoding RNAs(IncRNAs) and the molecular hallmarks of aging.** *Aging (Albany NY).* 2014; 6(12): 992–1009.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
36. **F** Kour S, Rath PC: **Long noncoding RNAs in aging and age-related diseases.** *Ageing Res Rev.* 2016; 26: 1–21.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
37. **F** Quinn JJ, Chang HY: **Unique features of long non-coding RNA biogenesis and function.** *Nat Rev Genet.* 2016; 17(1): 47–62.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
38. **F** Montes M, Nielsen MM, Maglieri G, *et al.*: **The lncRNA MIR31HG regulates p16<sup>INK4A</sup> expression to modulate senescence.** *Nat Commun.* 2015; 6: 6967.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
39. **F** Chen YN, Cai MY, Xu S, *et al.*: **Identification of the lncRNA, AK156230, as a novel regulator of cellular senescence in mouse embryonic fibroblasts.** *Oncotarget.* 2016; 7(33): 52673–84.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
40. Boon RA, Hofmann P, Michalik KM, *et al.*: **Long Noncoding RNA Meg3 Controls Endothelial Cell Aging and Function: Implications for Regenerative Angiogenesis.** *J Am Coll Cardiol.* 2016; 68(23): 2589–91.  
[PubMed Abstract](#) | [Publisher Full Text](#)
41. **F** Zhu S, Li W, Liu J, *et al.*: **Genome-scale deletion screening of human long non-coding RNAs using a paired-guide RNA CRISPR-Cas9 library.** *Nat Biotechnol.* 2016; 34(12): 1279–86.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
42. Fontana L, Partridge L, Longo VD: **Extending healthy life span—from yeast to humans.** *Science.* 2010; 328(5976): 321–6.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
43. Schumacher B, van der Pluijm I, Moorhouse MJ, *et al.*: **Delayed and accelerated aging share common longevity assurance mechanisms.** *PLoS Genet.* 2008; 4(8): e1000161.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
44. Corpas E, Harman SM, Blackman MR: **Human growth hormone and human aging.** *Endocr Rev.* 1993; 14(1): 20–39.  
[PubMed Abstract](#) | [Publisher Full Text](#)
45. Crimmins E, Vasunilashorn S, Kim JK, *et al.*: **Biomarkers related to aging in human populations.** *Adv Clin Chem.* 2008; 46: 161–216.  
[PubMed Abstract](#) | [Publisher Full Text](#)
46. Johnson SC, Rabinovitch PS, Kaeblerlein M: **mTOR is a key modulator of ageing and age-related disease.** *Nature.* 2013; 493(7432): 338–45.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
47. **F** Bajwa P, Nagendra PB, Nielsen S, *et al.*: **Age related increase in mTOR activity contributes to the pathological changes in ovarian surface epithelium.** *Oncotarget.* 2016; 7(15): 19214–27.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
48. Dieterlen MT, Bittner HB, Klein S, *et al.*: **Assay validation of phosphorylated S6 ribosomal protein for a pharmacodynamic monitoring of mTOR-inhibitors in peripheral human blood.** *Cytometry B Clin Cytom.* 2012; 82(3): 151–7.  
[PubMed Abstract](#) | [Publisher Full Text](#)
49. **F** Martin-Montalvo A, Mercken EM, Mitchell SJ, *et al.*: **Metformin improves healthspan and lifespan in mice.** *Nat Commun.* 2013; 4: 2192.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
50. Gordon SE, Lake JA, Westerkamp CM, *et al.*: **Does AMP-activated protein kinase negatively mediate aged fast-twitch skeletal muscle mass?** *Exerc Sport Sci Rev.* 2008; 36(4): 179–86.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
51. Massudi H, Grant R, Braidyn N, *et al.*: **Age-associated changes in oxidative stress and NAD<sup>+</sup> metabolism in human tissue.** *PLoS One.* 2012; 7(7): e42357.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
52. Dang W: **The controversial world of sirtuins.** *Drug Discov Today Technol.* 2014; 12: e9–e17.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
53. Imai S, Guarente L: **NAD<sup>+</sup> and sirtuins in aging and disease.** *Trends Cell Biol.* 2014; 24(8): 464–71.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
54. **F** Kim KS, Park HK, Lee JW, *et al.*: **Investigate correlation between mechanical property and aging biomarker in passaged human dermal fibroblasts.** *Microsc Res Tech.* 2015; 78(4): 277–82.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
55. **F** Zhang J, Fang L, Lu Z, *et al.*: **Are sirtuins markers of ovarian aging?** *Gene.* 2016; 575(2 Pt 3): 680–6.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
56. **F** Yudoh K, Karasawa R, Ishikawa J: **Age-related Decrease of Sirtuin 2 Protein in Human Peripheral Blood Mononuclear Cells.** *Curr Aging Sci.* 2015; 8(3): 256–8.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
57. Gorisse L, Pietrement C, Vuiblet V, *et al.*: **Protein carbamylation is a hallmark of aging.** *Proc Natl Acad Sci U S A.* 2016; 113(5): 1191–6.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
58. **F** Verbrugge FH, Tang WH, Hazen SL: **Protein carbamylation and cardiovascular disease.** *Kidney Int.* 2015; 88(3): 474–8.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
59. Semba RD, Nicklett EJ, Ferrucci L: **Does accumulation of advanced glycation end products contribute to the aging phenotype?** *J Gerontol A Biol Sci Med Sci.* 2010; 65(9): 963–75.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
60. Thorpe SR, Baynes JW: **Role of the Maillard reaction in diabetes mellitus and diseases of aging.** *Drugs Aging.* 1996; 9(2): 69–77.  
[PubMed Abstract](#) | [Publisher Full Text](#)
61. Hanssen NM, Wouters K, Huijberts MS, *et al.*: **Higher levels of advanced glycation endproducts in human carotid atherosclerotic plaques are associated with a rupture-prone phenotype.** *Eur Heart J.* 2014; 35(17): 1137–46.  
[PubMed Abstract](#) | [Publisher Full Text](#)
62. **F** Sayegh WN, Knight Iii PR, Guo WA, *et al.*: **Advanced Glycation End Products Induce Obesity and Hepatosteatosis in CD-1 Wild-Type Mice.** *Biomed Res Int.* 2016; 2016: 7867852.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
63. Brownlee M: **Advanced protein glycosylation in diabetes and aging.** *Annu Rev Med.* 1995; 46: 223–34.  
[PubMed Abstract](#) | [Publisher Full Text](#)
64. Nagai R, Shirakawa J, Ohno R, *et al.*: **Antibody-based detection of advanced glycation end-products: promises vs. limitations.** *Glycoconj J.* 2016; 33(4): 545–52.  
[PubMed Abstract](#) | [Publisher Full Text](#)
65. Dall'Olio F, Vanhooren V, Chen CC, *et al.*: **N-glycomic biomarkers of biological aging and longevity: a link with inflammaging.** *Ageing Res Rev.* 2013; 12(2): 685–98.  
[PubMed Abstract](#) | [Publisher Full Text](#)
66. Gleij DA, Goldman N, Lin YH, *et al.*: **Age-Related Changes in Biomarkers: Longitudinal Data from a Population-Based Sample.** *Res Aging.* 2011; 33(3): 312–26.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
67. Montoliu I, Scherer M, Beguein F, *et al.*: **Serum profiling of healthy aging identifies phospho- and sphingolipid species as markers of human longevity.** *Aging (Albany NY).* 2014; 6(1): 9–25.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
68. Sanchis-Gomar F, Pareja-Galeano H, Santos-Lozano A, *et al.*: **A preliminary candidate approach identifies the combination of chemerin, fetuin-A, and fibroblast growth factors 19 and 21 as a potential biomarker panel of successful aging.** *Age (Dordr).* 2015; 37(3): 9776.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
69. Syslová K, Böhmová A, Mikoška M, *et al.*: **Multimarker screening of oxidative stress in aging.** *Oxid Med Cell Longev.* 2014; 2014: 562860.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
70. **F** Shen EZ, Song CQ, Lin Y, *et al.*: **Mitoflash frequency in early adulthood predicts lifespan in *Caenorhabditis elegans*.** *Nature.* 2014; 508(7494): 128–32.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
71. **F** Tyrrell DJ, Bharadwaj MS, Jorgensen MJ, *et al.*: **Blood cell respirometry is associated with skeletal and cardiac muscle bioenergetics: Implications for a minimally invasive biomarker of mitochondrial health.** *Redox Biol.* 2016; 10: 65–77.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
72. **F** Tyrrell DJ, Bharadwaj MS, Van Horn CG, *et al.*: **Respirometric Profiling of Muscle Mitochondria and Blood Cells Are Associated With Differences in Gait Speed Among Community-Dwelling Older Adults.** *J Gerontol A Biol Sci Med Sci.* 2015; 70(11): 1394–9.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
73. **F** Wilkins HM, Koppel SJ, Weidling IW, *et al.*: **Extracellular Mitochondria and Mitochondrial Components Act as Damage-Associated Molecular Pattern Molecules in the Mouse Brain.** *J Neuroimmune Pharmacol.* 2016; 11(4): 622–8.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
74. Burton DG: **Cellular senescence, ageing and disease.** *Age (Dordr).* 2009; 31(1): 1–9.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
75. Campisi J: **Aging, cellular senescence, and cancer.** *Annu Rev Physiol.* 2013; 75: 685–705.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
76. Tacutu R, Budovsky A, Yanai H, *et al.*: **Molecular links between cellular senescence, longevity and age-related diseases - a systems biology perspective.** *Aging (Albany NY).* 2011; 3(12): 1178–91.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
77. **F** Sharpless NE, Sherr CJ: **Forging a signature of *in vivo* senescence.** *Nat Rev Cancer.* 2015; 15(7): 397–408.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
78. **F** Matjusaitis M, Chin G, Sarnoski EA, *et al.*: **Biomarkers to identify and isolate**



- senescent cells. *Ageing Res Rev.* 2016; **29**: 1–12.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
79. Dimri GP, Lee X, Basile G, *et al.*: **A biomarker that identifies senescent human cells in culture and in aging skin in vivo.** *Proc Natl Acad Sci U S A.* 1995; **92**(20): 9363–7.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
80. Liu Y, Sanoff HK, Cho H, *et al.*: **Expression of p16<sup>INK4a</sup> in peripheral blood T-cells is a biomarker of human aging.** *Aging Cell.* 2009; **8**(4): 439–48.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
81. Vandenberg B, Brouwers B, Hatse S, *et al.*: **p16<sup>INK4a</sup>: A central player in cellular senescence and a promising aging biomarker in elderly cancer patients.** *J Geriatr Oncol.* 2011; **2**(4): 259–69.  
[Publisher Full Text](#)
82. Kurz DJ, Decary S, Hong Y, *et al.*: **Senescence-associated (beta)-galactosidase reflects an increase in lysosomal mass during replicative ageing of human endothelial cells.** *J Cell Sci.* 2000; **113**(Pt 20): 3613–22.  
[PubMed Abstract](#)
83. Yang NC, Hu ML: **The limitations and validities of senescence associated-beta-galactosidase activity as an aging marker for human foreskin fibroblast Hs68 cells.** *Exp Gerontol.* 2005; **40**(10): 813–9.  
[PubMed Abstract](#) | [Publisher Full Text](#)
84. Schadendorf D, Möller A, Algermissen B, *et al.*: **IL-8 produced by human malignant melanoma cells in vitro is an essential autocrine growth factor.** *J Immunol.* 1993; **151**(5): 2667–75.  
[PubMed Abstract](#)
85. **F** Wajapeyee N, Serra RW, Zhu X, *et al.*: **Oncogenic BRAF induces senescence and apoptosis through pathways mediated by the secreted protein IGFBP7.** *Cell.* 2008; **132**(3): 363–74.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
86. Tchkonina T, Zhu Y, van Deursen J, *et al.*: **Cellular senescence and the senescent secretory phenotype: therapeutic opportunities.** *J Clin Invest.* 2013; **123**(3): 966–72.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
87. Coppé JP, Desprez PY, Krtolica A, *et al.*: **The senescence-associated secretory phenotype: the dark side of tumor suppression.** *Annu Rev Pathol.* 2010; **5**: 99–118.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
88. Bianchi ME: **DAMPs, PAMPs and alarmins: all we need to know about danger.** *J Leukoc Biol.* 2007; **81**(1): 1–5.  
[PubMed Abstract](#) | [Publisher Full Text](#)
89. **F** Huang J, Xie Y, Sun X, *et al.*: **DAMPs, ageing, and cancer: The 'DAMP Hypothesis'.** *Ageing Res Rev.* 2015; **24**(Pt A): 3–16.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
90. Wagner KH, Cameron-Smith D, Wessner B, *et al.*: **Biomarkers of Aging: From Function to Molecular Biology.** *Nutrients.* 2016; **8**(6): pii: E338.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
91. **F** Belsky DW, Moffitt TE, Cohen AA, *et al.*: **Telomere, epigenetic clock, and biomarker-composite quantifications of biological aging: Do they measure the same thing?** *bioRxiv.* 2016.  
[Publisher Full Text](#) | [F1000 Recommendation](#)
92. Chen W, Qian W, Wu G, *et al.*: **Three-dimensional human facial morphologies as robust aging markers.** *Cell Res.* 2015; **25**(5): 574–87.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
93. Chen W, Xia X, Huang Y, *et al.*: **Bioimaging for quantitative phenotype analysis.** *Methods.* 2016; **102**: 20–5.  
[PubMed Abstract](#) | [Publisher Full Text](#)
94. **F** Horvath S: **DNA methylation age of human tissues and cell types.** *Genome Biol.* 2013; **14**(10): R115.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
95. Cohen AA, Milot E, Yong J, *et al.*: **A novel statistical approach shows evidence for multi-system physiological dysregulation during aging.** *Mech Ageing Dev.* 2013; **134**(3–4): 110–7.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
96. Cohen AA, Li Q, Milot E, *et al.*: **Statistical distance as a measure of physiological dysregulation is largely robust to variation in its biomarker composition.** *PLoS One.* 2015; **10**(4): e0122541.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
97. De Maesschalck R, Jouan-Rimbaud D, Massart DL: **The Mahalanobis distance.** *Chemometr Intell Lab Syst.* 2000; **50**(1): 1–18.  
[Publisher Full Text](#)
98. **F** Putin E, Mamoshina P, Aliper A, *et al.*: **Deep biomarkers of human aging: Application of deep neural networks to biomarker development.** *Aging (Albany NY).* 2016; **8**(5): 1021–33.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
99. Bürkle A, Moreno-Villanueva M, Bernhard J, *et al.*: **MARK-AGE biomarkers of ageing.** *Mech Ageing Dev.* 2015; **151**: 2–12.  
[PubMed Abstract](#) | [Publisher Full Text](#)

# Open Peer Review

Current Referee Status:   

---

## Editorial Note on the Review Process

F1000 Faculty Reviews are commissioned from members of the prestigious F1000 Faculty and are edited as a service to readers. In order to make these reviews as comprehensive and accessible as possible, the referees provide input before publication and only the final, revised version is published. The referees who approved the final version are listed with their names and affiliations but without their reports on earlier versions (any comments will already have been addressed in the published version).

---

## The referees who approved this article are:

### Version 1

- 1 **Kristina Endres** Department of Psychiatry and Psychotherapy, University Medical Center of the Johannes Gutenberg University Mainz, Untere Zahlbacher Strasse 8, 55131 Mainz, Germany  
**Competing Interests:** No competing interests were disclosed.
- 1 **Alan Cohen** Groupe de recherche PRIMUS, Department of Family Medicine, University of Sherbrooke, Sherbrooke, Quebec, Canada  
**Competing Interests:** No competing interests were disclosed.
- 1 **Eileen Crimmins** Davis School of Gerontology, University of Southern California, Los Angeles, California, USA  
**Competing Interests:** No competing interests were disclosed.