The concept of the epigenetic clock and its economic stakes

1. What is the epigenetic clock?

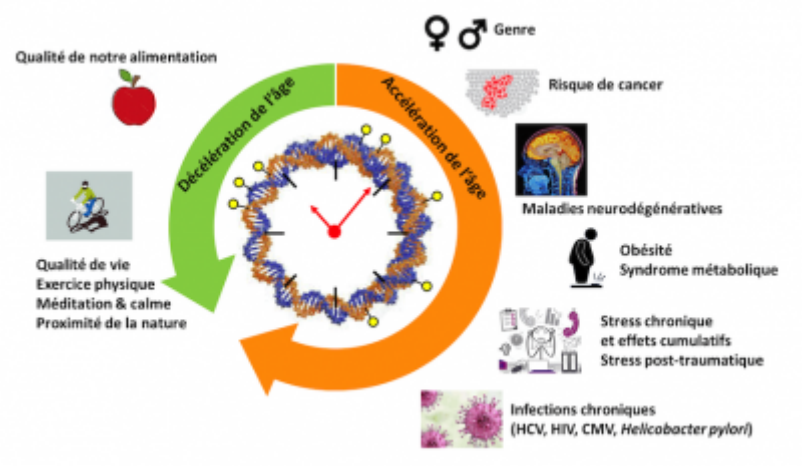

Figure 1. The epigenetic clock: the epigenome evolves throughout an individual's life, according to complex dynamics [Source: after Quach A, et al., ref. 1] - DOI:10.18632/aging.101168]

The epigenome (Read Epigenetics: the genome and its environment) evolves over the course of an individual's life, which is known as the **epigenetic clock** (Figure 1) [1]. Depending on the case, certain sites in the genome become increasingly methylated or demethylated over the years. About ten years ago, researchers identified a series of "age-related" genes (in particular genes involved in DNA replication and nuclear organization, etc.). From the methylation profiles of these genes, it is then possible to determine the "epigenetic age" of an individual. In some individuals this age may be higher than their chronological age, and their life expectancy may be reduced.

For example, the epigenetic clock of some individuals is accelerated compared to others, which is associated with an increased risk of chronic disease and mortality [2]. It is not yet known whether this epigenetic clock is a cause or a consequence of ageing; however, its accuracy and predictive power of the individual's health status offer the possibility of accurately assessing the effectiveness of lifestyle interventions (changes in nutritional habits, regular physical exercise, stress management...). In other words, the risk of morbidity/mortality depends on epigenetic age, which may be out of sync with chronological age.

By assessing a series of risk factors (environmental and behavioral related), Steve Horvath as early as 2016 [2] created an algorithm currently relying on more than 2000 specific CpG sites (cytosine residue methylation sensitive sites) that would be markers of aging (cf. above) of an individual and his probability of suffering from a pathology (metabolic stress, obesity, sensitivity to atmospheric pollutants, chronic infectious diseases, chronic psychological stress) (See Epigenetics: the genome and its environment). He has therefore deduced a tool for predicting the time left to live. The researchers in his group tested his biological clock concept on blood samples taken from more than 10,000 subjects with known dates of death to demonstrate the effectiveness of his method. He discovered:

- That a diet rich in fish, fruits and vegetables tends to decrease epigenetic age;
- That heavy smokers have a certain type of methyl group indicating a more advanced biological clock;

Figure 2. A diet rich in, fruits and vegetables tends to decrease epigenetic age. [Source: Bill Branson (Photographer), Public domain, Wikimedia Commons]

That lack of sleep, stress or alcohol would also have detrimental effects.

It appears that epigenetic clocks are more accurate than chronological age in estimating biological age. Finally, a recent study by his group [3] demonstrates that epigenetic aging could be slowed or even reversed in humans with balanced hormonal therapy:

1. In this study, nine healthy men, aged 51 to 65, took a synthetic growth hormone known to regenerate the thymus, an organ of the immune system that atrophies with age, for one year.
2. From blood samples taken before and after the experiment, the scientists then determined the volunteers' "epigenetic" age (based on the position of "molecular tags" - methylations - located on the DNA).
3. In addition to protective immunological changes and improved risk scores for many age-related diseases, the researchers observed an average epigenetic age that was about 1.5 years younger than the initial value.

But since then, other studies have sought to identify other markers of ageing such as telomere reduction [4] and methylation profiles of subtelomeric regions [5] (See Focus on slowing down ageing: the telomerase pathway?).

2. The epigenetic clock at the service of insurance companies and police institutions?

The estimation of the epigenetic clock appears to be a new platform for biological tests that is of interest not only to the scientific community, but also to private insurance companies (USA) to refuse certain benefits because of telomeres that are too short or because the methylation profile is too high. These tests could also be used for non-medical purposes, such as in immigration cases to prove the age of undocumented refugees seeking asylum as minors. Some facts:

- GWG, the parent company of *Life Epigenetics* (now FOXO bioscienceÓ), manages more than $1.5 trillion in life insurance policies on behalf of investors. Steve Horvath's algorithm could prove to be a considerable competitive advantage to better estimate the profitability of their contracts. This insurance company thus holds the exclusive license to the method, including the patent that belongs to the University of California at Los Angeles (UCLA). In 2017, it sent saliva sampling kits to its underwriters and hopes to make epigenetics central to its strategy. The company recently announced that it would test the epigenetic age of its customers to classify them into risk groups.
- In late 2017, Israeli startup *Clew MedicalÓ* announced the development of an algorithm to predict how fast an individual's health will worsen based on hundreds of data points. It hopes to sell its technology to hospitals, with the official aim of identifying at-risk patients before their condition worsens too much and "warn the family when the end is near."
- *Aspire HealthÓ*, another start-up acquired by homecare giant *AnthemÓ*, also claims to be able to identify whether a patient is going to die within a year.
- Other companies such as *ChronomicsÓ* and *MyDNageÓ* have begun selling epigenetic age tests online. *Kobor Lab* recently developed the first pediatric epigenetic clock designed to determine the age of children (see below), which could be used in the medical field (forensics) and for research. [6]

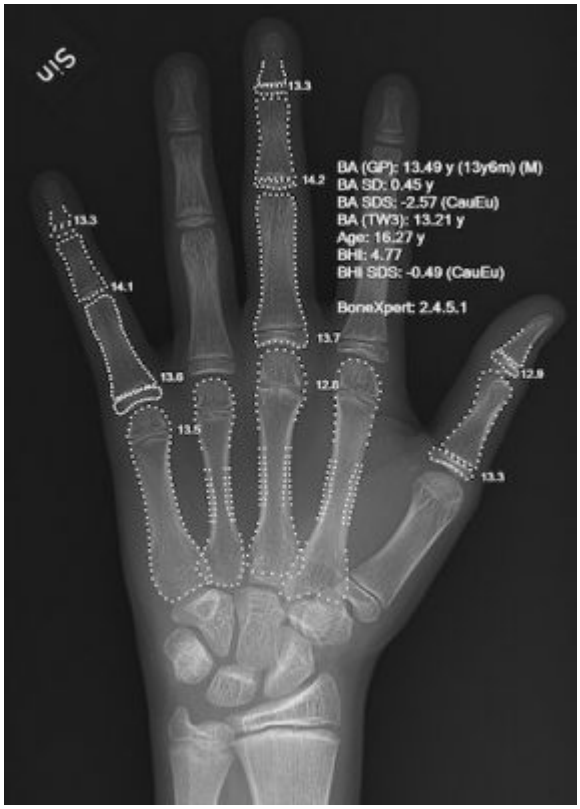

Figure 3. 16.27 year old male hand X-ray with automatic bone age calculation taken due to delayed puberty. The bone age determined by the tests is lower: two different algorithms give values of 13.21 and 13.49. [Source: Mikael Häggström, CC0, via Wikimedia Commons]

Authorities say that because of the advantages of being considered minors, some unaccompanied refugees claim to be younger than they actually are. But the anatomical tests currently used to assess age [7] have an error range of up to 3 to 4 years (Figure 3). Studies are also underway to assess how the various ethnic backgrounds of European refugees might influence the epigenetic clock. One can imagine other future applications, such as monitoring child labor and trafficking, or even identifying youth fighting in armed conflicts.

Finally, in addition to markers linked to the epigenetic clock, there are tests that can be used to estimate the "cellular" age of clients: e.g., the tests proposed by *Life LengthÓ* or *SpectraCell LaboratoriesÓ*, measuring the length of telomeres in blood cells. The technology is based on the Q-Fish fluorescence method [4]. According to the company, the fluorescence intensity is representative of biological age. According to these private companies, the target clientele is patients who want to know if they will live long or not... Scientists are already concerned about the use that may be made of this indication by ill-intentioned people, trying to take advantage of it to sell anti-aging miracle products.

3. Epigenetics and "epigenethics"

The epigenetic clock, conceived as epigenetic estimators of age and aging, could provide a better understanding of the biological pathways underlying the development of disorders associated with aging and devise biomedical and/or social interventions to prevent, reverse, or mitigate them. Assessing the epigenetic age of different cell types also provides an opportunity to study how environmental stressors, or decreased social and dietary levels, may contribute to such disorders through accelerated epigenetic aging. In addition to their potential clinical and public health applications, these (epigenetic or telomeric) estimators of age and aging may be used for non-medical purposes by insurance companies and police in immigration policy. There is an urgent need to discuss the potential ethical, legal and social implications of non-medical uses of epigenetic clocks. We argue that a human rights framework should guide future discussions of these important and situational issues. [8]

Read more

- Fraga MF, Esteller M. Epigenetics and aging: the targets and the marks. Trends Genet. 2007 Aug;23(8):413-8.
- Levine ME, et al. An epigenetic biomarker of aging for lifespan and healthspan. Aging (Albany NY). 2018 Apr 18;10(4):573-591.
- Hu H, Li B, Duan S. The Alteration of Subtelomeric DNA Methylation in Aging-Related Diseases. Front Genet. 2019 Jan 9;9:697. doi: 10.3389/fgene.2018.00697

- Bacalini MG et al. Ageing affects subtelomeric DNA methylation in blood cells from a large European population enrolled in the MARK-AGE study. 2021 Apr 19. doi: 10.1007/s11357-021-00347-9
- Abbott A. European scientists seek 'epigenetic clock' to determine age of refugees. Nature. 2018 Sep;561(7721):15. doi: 10.1038/d41586-018-06121-w.
- Abbott A. Can epigenetics help verify the age claims of refugees? Nature 2018 Nature **561**, 15 https://doi.org/10.1038/d41586-018-06121-w
- Dupras C, Beauchamp E, Joly Y. Selling direct-to-consumer epigenetic tests: are we ready? *Nat Rev Genet.*2020 Jun;21(6):335-336. doi: 10.1038/s41576-020-0215-2.

Notes and references

Cover image. Source: [Source: royalty free / PxHere]

[1] Quach A, *et al*. (2017). Epigenetic clock analysis of diet, exercise, education, and lifestyle factors. *Aging* (Albany NY) 9:419-446

[2] Horvath S. & Raj K. (2018) DNA methylation-based biomarkers and the epigenetic clock theory of aging. *Nat Rev Genet* 19:371-384

[3] Fahy GM *et al.* (2019) Reversal of epigenetic aging and immunosenescent trends in humans. *Aging Cell*. 18(6):e13028. doi: 10.1111/acel.13028

[4] Measured with the Q-Fish (quantitative fluorescence *in situ* hybridization) technique where a fluorescent probe binds to telomeres in a manner proportional to their length.

[5] Subtelomeres form the transition between chromosome-specific sequences and terminal telomeric repeats.

[6] McEwen LM *et al.* (2020) The PedBE clock accurately estimates DNA methylation age in pediatric buccal cells. *Proc Natl Acad Sci117*(38):23329-23335.

[7] They are based on the use of X-ray and magnetic resonance imaging. This method "allows us to assess with a good approximation the developmental age of an adolescent under fifteen years of age"; however, there are "difficulties" in determining an age "in both sexes beyond fifteen years of age, especially in boys", the National Academy of Medicine estimated in 2007. "Bone tests are only reliable when we are very far from the age of majority," André Deseur, vice-president of the French Medical Association, recently declared in Libération.

[8] Charles Dupras *et al.* (2019) Potential (mis)use of epigenetic age estimators by private companies and public agencies: human rights law should provide ethical guidance*, Environmental Epigenetics* 5, 3, dvz018, https://doi.org/10.1093/eep/dvz018