Podcast Episode 12: Measuring biological age – a genetic self-test

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Teaser

Hey everyone! Welcome to the new episode of the Life Extension Podcast – technology & magic, society & business. The life extension industry has provided us with a new gadget: the epigenetic clock. This episode addresses consumers considering to measure their biological age. Continue listening to learn about DNA methylation, biomarkers for aging, controversial applications, and why measuring biological age may be more important to the life extension industry than actual treatments. Last you might be interested in hearing why I consider my self-test a rather disappointing experience.

In this episode I will discuss measuring biological age. Several suppliers have started to market genetic tests for consumers allowing to track biological age compared to chronological age. In short, a consumer can find out how young her body actually is compared to her age in terms of years since birth. This is of course interesting information about ourselves: how well are we keeping up with age, what impact does our lifestyle or our diseases have on our life expectancy, how to quantify risk factors or beneficial changes in lifestyle in terms of years to live? In order to understand more about this subject I have been reading about the biochemical processes behind these genetic tests, and I have actually ordered a genetic test myself.

Anyone can order these test kits. They cost in the range between 200 to 500 USD from US suppliers. I bought mine from a German supplier, which was priced at around 200 EUR, and which cost me 155 EUR after a promotional discount. The test was very easy to do. Just take a saliva sample using the provided test kit and mail it to the laboratory for processing. After activating the test online, I was asked a number of questions about my personal lifestyle. The supplier promised the test result within a few days, although I had to wait for 1 month, probably due to the Covid lock-down. The test procedure was well-explained, and the entire consumer experience was smooth and hassle-free. The test report however came as a surprise in the sense of how little content it contained. Or rather it told me one single number, which is that biologically I am 5 years younger than my official, or chronological age. It mentioned that this number has been calculated by automatic, science based processes measuring DNA-methylation. In addition it kind of flagged out which of my behaviors may have had positive or negative influences on my genetic test result. E.g. I indicated in the questionnaire that I do regular exercise and found that mentioned in the test report as a positive factor. Same with all other questions. So the test report consisted mainly in repeating my own replies to the supplier's lifestyle questions and providing me with needless evaluations if my behaviors are beneficial or not. In addition I was given a set of extremely general recommendations about exercise, nutrition, stress avoidance, and environmental factors. That was really disappointing! This leaves as the only tangible result that fateful number, the information that I have aged 5 years less than to be expected by my birth date. Nothing else.

Obviously, I wanted to know more about the scientific base of that test, as well as the assumptions in calculating that number. So I have sent various questions to the supplier. I was offered a free 15min health consultation on the phone, which I was able to book online 1 week later. During the call the service representative tried to reply to my questions, which I have forwarded to her beforehand, but she was not able to answer any of them in a satisfactory way, even though she had discussed them with colleagues beforehand. It became obvious that the supplier was only a sales & marketing organization without scientific knowledge. It appeared from the phone call that not even the laboratory, which conducts the analysis, would know much more. They just implement a procedure which has been developed by a research institute.

So let's dig into the science behind measuring biological age through DNA methylation: Methylation is when a methyl group is added to a DNA molecule in a biochemical process. There are specific gene areas, called CpG islands, which consist of a high proportion of those nucleobases to which methyl groups can connect. When CpG islands, which are located in the promoter region of a gene, get methylated, then gene transcription becomes deactivated – the gene is switched off. As such DNA methylation is part of the epigenetic regulation. As a reminder in case you forgot your biology classes: genes encode proteins, but an important mechanism, called epigenetic regulation, is responsible to switch genes on or off. DNA-methylation could be understood as tagging bits of information to the DNA without actually changing DNA. DNA-methylation also plays a few other roles, but let's not get into that.

The function which interests us most in the context of life extension as our podcast's topic is that DNA-methylation of CpG islands naturally increases with age and can therefore serve as a biomarker for aging. It can be used to determine biological (aka epigenetic or phenotypic) age compared to chronological age. Methylation patterns of DNA can actually predict aging and mortality of basically any cells, tissues, or organisms. The technique of reading and interpreting age-related methylation patterns is called the epigenetic clock. It has first been developed by Steve Horwath, but several other versions exist by now.

There is already much evidence that methylation patterns are strongly associated not only with overall lifespan, but also with specific risk factors and diseases, lifestyle and behaviors, educational background (Horwarth 2018, Ecker 2019), and even clinical parameters. So an increased cholesterol measurement, a smoking habit, or eating fish may be reflected in the methylation pattern (Mendelsohn 2018 – referring to a study by Roetger et al., 2018).

Let's now talk about the potential use of epigenetic clocks. Most of all epigenetic clocks could become significant for the life extension industry in providing scientists with a yardstick. Because biological age can be subject to acceleration and deceleration compared to chronological age, epigenetic clocks could be used for identifying and testing anti-aging treatments in the laboratory and in individual patients. Even the impact of changed behaviors or environments could be measured. Epigenetic clocks can therefore be used as biomarkers for predicting outcome of anti-aging interventions. For example a trial study of testing age-related effects after administering certain drugs found a reversal of the epigenetic clock by 2 ½ years in trial participants, indicating a possible rejuvenation effect of the treatment (Abbott

2019). Epigenetic clocks could be used as a biomarker for individualized strategies incl personalized medicine, preventive healthcare and lifestyle changes to avoid specific disease conditions and to increase life span (Ecker 2019).

Life extension interventions are the bright side of epigenetic clock applications as an easy measurement of biological age. But there are also possible applications in insurance, forensics, and immigration. Will insurance companies be allowed to assess individual mortality or morbidity risks when calculating insurance fees? Or can an illegal immigrant without ID be deported based on his age as determined by a genetic test? Society will need to discuss if such applications are deemed permissible or not (Ecker 2019).

Research on epigenetic clocks has not reached final conclusions yet. Although there are clear associations between methylation patterns of DNA and aging, the detailed cause-effect relationships of molecular mechanisms are not really understood. This is why epigenetic clocks seem to be good biomarkers for overall aging. But different reasons for diseases, longevity, or death cannot be distinguished yet (Horwarth 2018, Ecker 2019, Fransquet 2019). We don't even know if methylation is actually the cause or the effect of aging. So far the epigenetic clock is still a mystery (Ecker 2019).

Unfortunately, epigenetic clocks also have a few other important shortcomings, which test providers usually don't talk about. They are related to how epigenetic clocks are designed, or rather by which method. The process of constructing the epigenetic clock depends on machine learning techniques, which creates a kind of a black box. The relation between input and output makes some sense, but we don't know what happens inside.

Algorithms of epigenetic clocks are the product of machine learning techniques which were trained on tissue samples. A small number of CpG islands is chosen by the machine learning process, which are later used to generate methylation patterns, based on which the algorithm is to calculate biological age. But neither the machine learning technique nor the algorithm have any knowledge about those CpGs and the genes to which they belong. The same weaknesses of any statistical operation are obviously present in machine learning techniques as well. On average it seems to work, even without knowing why. But insights about the specifics cannot be expected. Methylation measurements at individual CpG sites are consistently unreliable due to technical variance (or noise). They showed technical variation of up to 3 to 9 years when tested again on the same samples, which is obviously problematic when evaluating interventions which are supposed to reduce biological age by let's say 2 years (Higgins-Chen at al. 2021).

Another issue which suppliers of genetic tests don't mention in their marketing brochure, is that results from different epigenetic clocks are not comparable due to their different design. Depending on which tissue samples were submitted to the machine learning process, the resulting algorithm will tend to be tissue-specific (Shireby 2020). One is better in its correlation to a specific phenotype, another in its correlation to overall chronological age of the organism. One predicts accurately time to death, another one time to disease.

A meta-analysis of a larger number of science papers on epigenetic clocks as predictor of disease and mortality risks has found substantial variation of measurements, meaning that so far epigenetic clocks are still not as reliable as we would like them to be, although the fact of association between methylation and mortality or disease is not being doubted. Unfortunately, longitudinal studies observing DNA-methylation over time and how they are impacted by diseases, lifestyle changes, and changes in environment, are still missing. The same meta-analysis also warned that many of the reviewed science papers were presenting results as overly positive in order to be accepted for publication (Fransquet 2019).

After reading quite a bit of scientific literature on the topic, it appeared to me that the number presented to me as my biological age must certainly have some relational value compared with various factors of aging, but it is certainly a very dynamic number – in the way it has been generated, and also with regards to what it could mean.

Let's conclude this episode with a final evaluation of my experience in measuring my biological age with a genetic self-test. First of all, we should be clear, that these tests are consumer products. Packaging, marketing messages, promised benefits, price points, and user experience all define it as a consumer product trying to connect with our psychological disposition and to compete for a share of our wallet. But as a consumer, what did I actually get out of this test? Mainly I obtained a single number, called my biological age, as a high-level aggregate of a large set of parameters of my life, of what I actually am. For the argument's sake, let's put aside the technical questions about reliability and unknown cause-effect relations of the test, except that there is obviously still room for improvement. The most relevant question is, what is the value of testing my biological age through DNA methylation, if I can know the result already based on my history, my lifestyle, my education level, my body mass index, blood pressure, and cholesterol check? To whom is this sort of quantification and reduction to a single number of a personal life useful: only to people or institutions who would like to know me better like e.g. insurance companies. But is it useful to us as health-conscious consumers? It fits into the culture of the quantified self. After tracking our fitness, we perhaps want to track our life as well, creating more data, because data is fashionable. Perhaps we want to know that number to compare ourselves with others. But I doubt that this test is necessary for people who already know what they are doing. However, at times when some self-reflection is required, the test might provide a helpful point of reference. Perhaps it is useful as a wake-up call in the face of unhealthy habits, or just as a symbolic confirmation of positive lifestyle changes over time.

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