TruDiagnostic™
The Epigenetic Company

Reveal Your TruAge™

Collection Results Report

Hi John,

Thank you for taking the TruAge test by TruDiagnostic. TruDiagnostic is a company that has been built on *one premise*. We want to be able to read your DNA methylation patterns so that we can help you live a longer, better quality life. In the report below, we will explain everything about our test including why it is important and how you can use this metric to live a healthier life.

By using TruAge, you have now unlocked a lifetime of information about yourself. As we get better at reading each methylation spot on your DNA, and the outcomes that each spot is correlated to, we will continue to update you on this information and what it tells us about you. You are one of the first to have your DNA read and interpreted by our innovative algorithms. We are thankful that you are adding to the growing science and innovation around these areas.

Hopefully this will be the first of many times we report those metrics and outcomes to you so we can help you unlock a longer, healthier life.

Thanks,
The TruDiagnostic Team

TABLE OF CONTENTS

WHAT IS EPIGENETICS

and how is it different than genetics?

Epi - is a greek prefix for "above". ***Genetics*** is the study of our DNA. Together, epigenetics is defined as study of things above and beyond the genome. This means we are analyzing the changes to your DNA and how it actually affects the body instead of what the DNA could possibly do or mean.

It is often more useful than genetics because it allows us to see behavior of genetic material, not just what it contains. Traditional genetics is like looking at a light bulb and its components but not knowing if light is produced. Epigenetics lets us know if the light bulb is on or off.

The link between epigenetics and health is through biological age. ***This is important because aging is THE leading risk factor for multiple chronic diseases and disorders and can be measured by epiclock.*** Therefore, finding a way to slow the biological aging process is essential. Through epigenetics, TruAge does just that. Our epigenetic clock is the most accurate measurement of biological age and age-related disease risk.

Epigenetic aging can be reversed, therefore it is crucial to understand DNA methylation changes by utilizing TruAge. We can apply changes to our lifestyles by using TruAge to show that we are reducing YOUR risk of incidence of disease and death.

Genetic Testing **VS** Epigenetic Testing

	23andMe and Similar Testing	TruAge™
Measures the Genetic Code	✓	
Reports Health Risks	✓	✓
Measurement of How Genes Are Expressed		✓
Able to Influence with Lifestyle Changes		✓
Unique Algorithms For Health Insights		✓
Measures a Value that You Can Improve Over Time		✓

WHAT IS BIOLOGICAL AGE

and why is this important to know?

Everyone knows their chronological age. Chronological age is the number of candles that are on top of your cake and the birthdays that you celebrate (or sometimes don't!). However, developments in science have created another measurement of age called biological age. This measurement of age is based on years of statistical research which can predict how healthy you are and even when you might pass away.

The novel DNA biomarker uses markers on your DNA called methylation to predict your age. Your biological age is more accurate at predicting healthspan (how healthy you are) and lifespan (how long you will live) than any previous molecular biomarker. This can be correlated to aging-related conditions such as Alzheimer's disease and cancer. Ideally, everyone would want their biological age to be less than their chronological age. This means that you are living a healthy lifestyle that will help prevent sickness and disease longer.

Biological age is a single metric that takes all the important health data (weight, sex, medication, exercise frequency, etc.) about an individual and is able to report back how healthy you are.

CHRONOLOGICAL AGE

The number of years that have passed since birth. This cannot be influenced by lifestyle and eating habits.

BIOLOGICAL AGE

How old our cells really are, therefore, our real age. This can be reversed by attending to your health.

WHY IS THIS IMPORTANT?

When we are born, all of our cells have the same DNA. The cells in your eyes have the same DNA as the cells in your nails. ***So what makes our cells different?***

Each cell chooses to turn on some genes and turn others off. Your eyes express different genes than your hair. This is called expression, and it is controlled by the markers we measure with our TruAge test. Unfortunately, as we age, expression can become much harder to regulate as well and you start to lose function. In fact, aging is defined as the progressive loss of function. So, what does this have to do with biological age measured by TruAge?

TruAge can report how old your cells and DNA look, meaning you can measure how likely you are to develop disease or how long you might live.

It can be diffucult to measure your level of health. Health providers measure blood levels like cholesterol, inflammation, and blood sugar. They perform tests such as colonoscopies, vision tests, and physical function tests. Now, with this single measurement, you can link your health and longevity to a single, simple test which can help you and your health provider know the best way to address your health concerns in a personalized way.

Why are **METHYLATION MARKERS** a better measurement of Biological Age than other factors?

A recent review of six types of potential biological age estimators:

- Epigenetic Clocks
- Telomere Length
- Transcriptomic-Based
- Proteomic-Based
- Metabolomic-Based
- Composite Biomarkers

The study concluded that the ***epigenetic clock is the most promising molecular estimator of biological age.***[1]

Similarly, a comparative review of different ***forensic methods for age estimation concluded that DNA methylation is the most promising age-predictive biomarker.***[2]

Source:

1. Jylhävä, Juulia, et al. "Biological Age Predictors." EBioMedicine, vol. 21, 2017, pp. 29–36., doi:10.1016/j.ebiom.2017.03.046.

2. Lee, Hwan Young, et al. "Forensic DNA Methylation Profiling from Evidence Material for Investigative Leads." BMB Reports, vol. 49, no. 7, 2016, pp. 359–369.

HOW WAS THIS TEST CREATED and is it accurate?

WE LOOK AT OVER 900,000 PLACES ON THE DNA. HOW DO WE MAKE SENSE OF WHAT WE FIND?

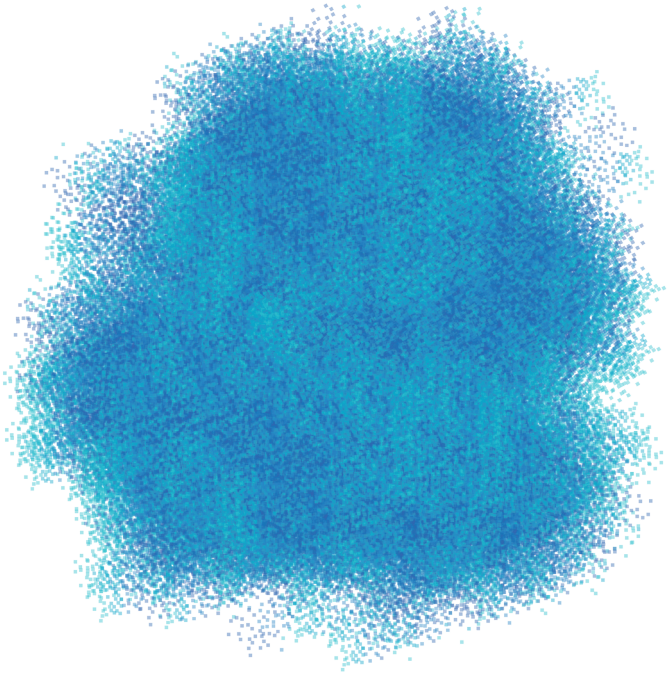
We have the most robust testing available in the world for biological age. The data we get from your DNA is 40,000 times larger than many competitors. But how do we know how this data applies to your health?

The answer is that we use a mathematical model built by computer learning and artificial intelligence. This model helps us design a powerful algorithm, by looking at all the data points. Thus far, we have given it almost a million data points from over 15,000 patients. We input variables such as blood tests, imaging data, genomic data, proteomic data, transcriptomic data and other bits of health history.

By analyzing the data, correlations are found with incredibly high accuracy and variables are linked to health outcomes. If 2000 patients show methylation on their DNA at the same place, and 1999 of those patients develop Alzheimer's, we can say with a high degree of certainty that that location on the DNA can help predict risk of Alzheimer's.

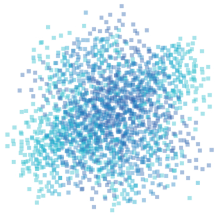
These mathematical calculations have been performed with biological aging. By comparing the biological and chronological age of a person, we can predict their risk of many different diseases and estimate time of death.

900,000 PLACES ON THE DNA



VS

2,500 POINTS COMPETITORS LOOK AT



YOUR EPIGENETIC AGE

Summary

INTRINSIC AGE

43.21

5 YEARS

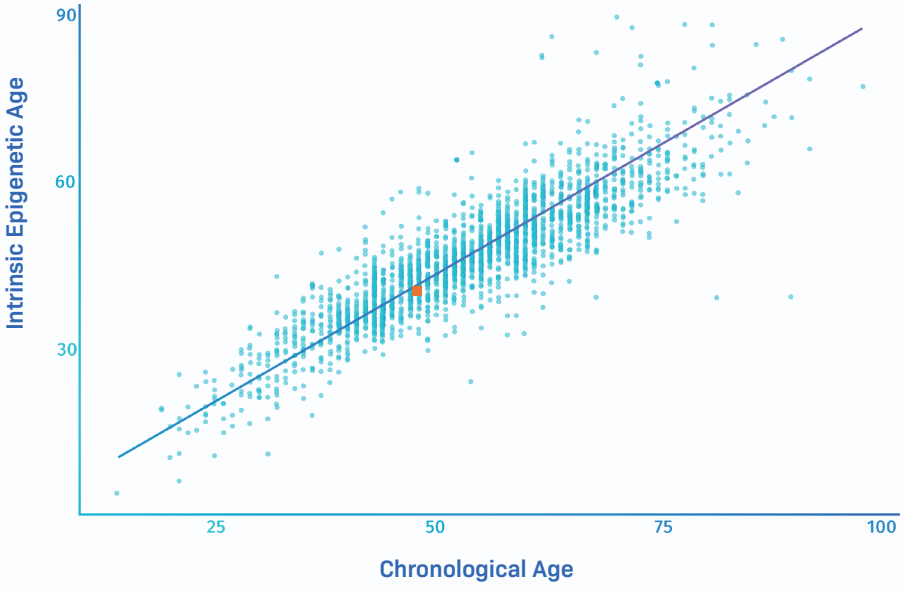
Age 0 — Age 100

38.21

CHRONOLOGICAL AGE

TruAge IEAA=3.45

You versus the Population



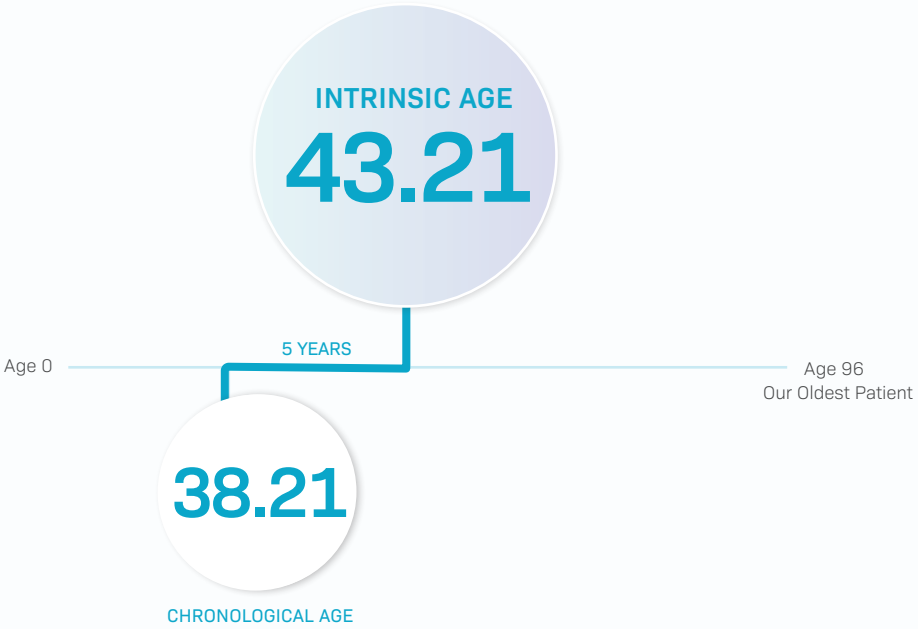
42.88

This is your Intrinsic Epigenetic Age using our previous (not Principle Component Analysis corrected) algorithm.

Read further to see explanations for each of your results.
Also, see **Your Treatment Framework on pg 63**.

YOUR BIOLOGICAL AGE

vs Chronological Age



Your biological age is higher than your chronological age.

This is the first of hopefully many tests to measure the status of your DNA. You are older than your DNA. While tests like 23andMe might predict risk of certain diseases, TruAge can see how much your DNA can be changed through proper lifestyle changes.

If your intrinsic age is much higher than your chronological age, don't worry. There are plenty of things you can do to slow your aging. If your intrinsic age is under your chronological age, don't stop doing what you are doing, but implemebt additional benefits.

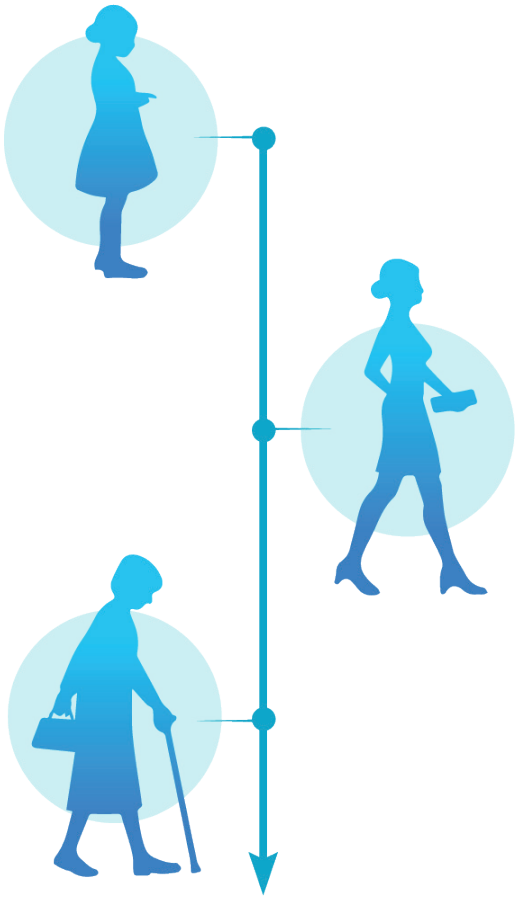
TERMS YOU SHOULD KNOW

IEA (INTRINSIC EPIGENETIC AGE) AND THE LINK TO IMMUNOSENESCENCE

As we age, we have changes other than what happens epigenetically on our DNA. One of the biggest changes to our health and body is called immunosenescence. Immunosenescence is when our immune system becomes weaker and less functional as we age. This is often seen in the blood by having a fewer number of naive T Cells and a higher number of senescent T Cells. There are other changes in the number and percentage of cells that make up the blood as well, and because of these changes, we see health consequences like older individuals being more likely to die from the flu or COVID-19. [53]

Because the DNA of these cells are found in unequal proportions as we age, we often want to control for this.

Therefore, IEA, intrinsic epigenetic age, is when we factor the change of these cell types out of the equation. In scientific terms, the measure of IEA measures "pure" epigenetic aging effects that are not confounded by differences in blood cell counts. [64]

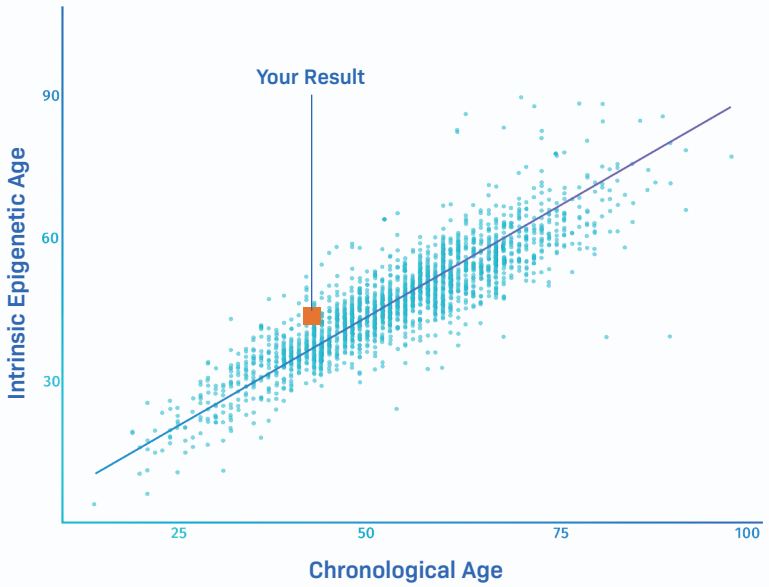


EEA (EXTRINSIC EPIGENETIC AGE)

Extrinsic Epigenetic Age (EEA) is when we factor immune cells back into the equation. Scientifically put, EEA tracks both age-related changes in blood cell composition and intrinsic epigenetic changes. [11]

In the rest of this report, you will see these two terms mentioned as they are both useful markers for health. Although intrinsic measures seem to exhibit greater consistency across cell types and organs, extrinsic measures seem to be better suited for assessing age-related decline of tissue performance as they exhibit stronger predictive associations with time to death than intrinsic measures of age.

HOW DO YOU COMPARE
to the general population?



Your Biological Age Compared to the General Population

This graph shows you where most people would range when comparing their chronological age versus their biological age.

One thing to remember is that a majority of our patient population are receiving this test in a preventative, integrative, functional medical community. As a result, our population metrics might be slightly different than those of the true general population. That is because often, the individuals who are being tested can afford the test and are most likely interested in aging in a healthy manner. In order to avoid this bias, TruDiagnostic actively recruits participants outside of this population to make sure we have a good snapshot of all variables such as socioeconomic status, race, gender, nationality and many others. If you have a connection to a under represented group who would like to be involved in this research, please let us know.

IS AGING A DISEASE?

Most scientists and medical professionals describe aging as *"a persistent decline in the age-specific fitness components of an organism due to internal physiological degeneration."* [24] The longstanding question," *if old age is itself a disease?*", has been addressed since ancient times. The Roman playwright Terentius, claimed "senectus ipsa est morbus" (old age itself is a disease), and Cicero, who some decades later argued in De Senectute: "pugnandum, tamquam contra morbum sic contra senectutem" (we have to fight against aging, as we do against a disease). These quotations elegantly summarize a long-held view of aging and old age.

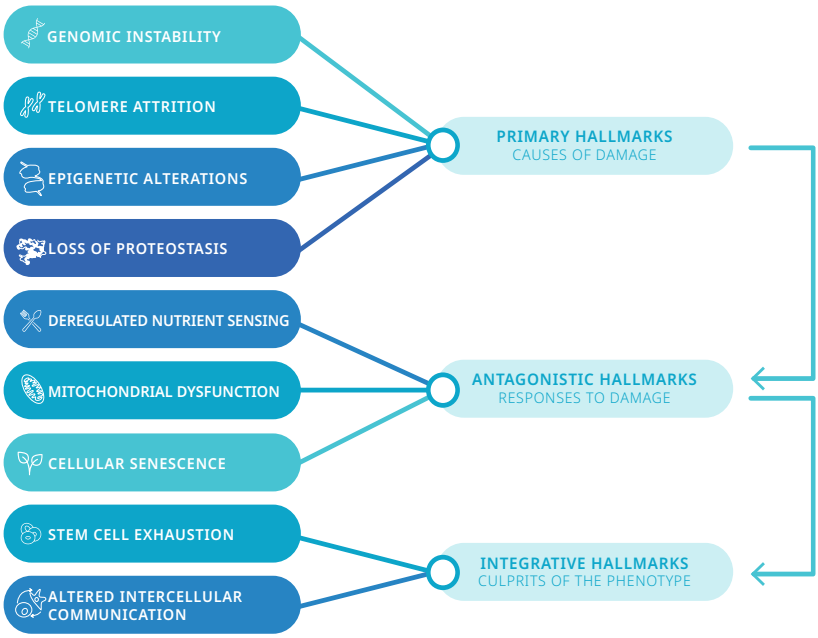
Aging is the predominant risk factor for most diseases and conditions that limit healthspan. Interventions in animal models that end up in an extension of lifespan often prevent or delay many chronic diseases. Why? For many years, aging, per se, is a physiological condition, which favors the onset of many diseases. However, the relationship is likely much more complex. Usually scientists say this relationship is related via 8 (or 9) hallmarks of aging. [43]

Hallmarks of Aging: TruDiagnostic is actively investigating how all of these hallmarks might affect the TruAge Epigenetic aging rate.

Aging is a target of optimal health due to it being the predominant risk factor for most diseases and conditions that limit lifespan.

Additionally, the specificity and accuracy of epigenetic tests make this a reliable metric to judge health by limiting aging and therefore reducing the major risk factors for disease. The World Health Organization recently added a code to identify diseases linked with aging.

We don't believe that aging is required. You can alter the aging process in your own body. We want to help you with that process.



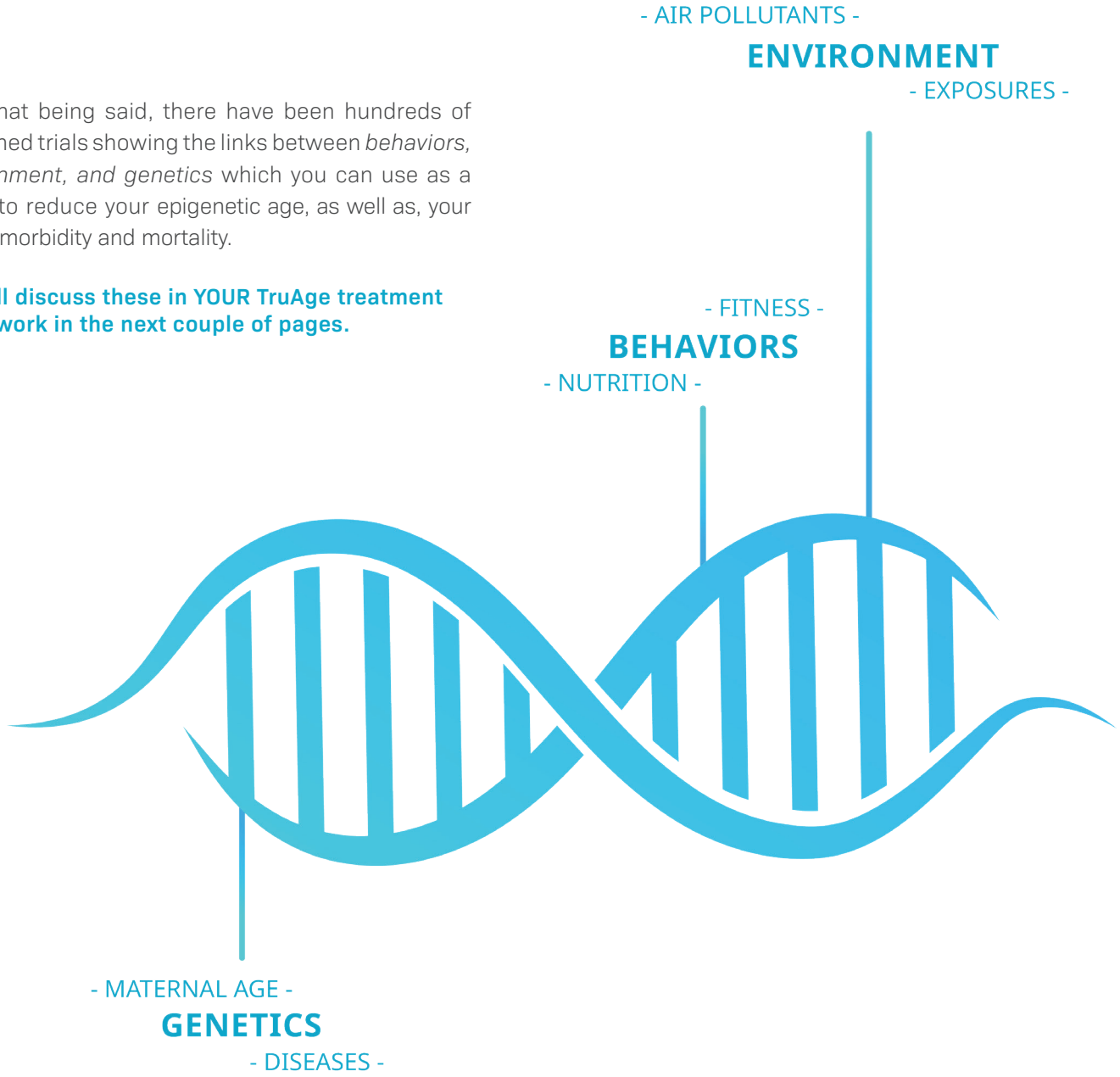
HOW DO I SLOW MY AGING?

WHAT DOES THE DATA SAY?

Unfortunately, the data around slowing epigenetic age is very new. While this means you are on the cutting edge of medical therapy, it also means that interventions to help reverse your epigenetic age are still being investigated.

With that being said, there have been hundreds of published trials showing the links between *behaviors, environment, and genetics* which you can use as a guide to reduce your epigenetic age, as well as, your risk of morbidity and mortality.

We will discuss these in YOUR TruAge treatment framework in the next couple of pages.



TREATMENT FRAMEWORK

"60% of the determination of the aging rate is due to factors that you can control!"

We have created a treatment framework to let you see the biggest areas that affect your aging. Much like your epigenetics, this framework is constantly updating and changing. We will continue to update your treatment framework with new results that are available and provide suggestions on how to age better. *This framework will be utilized to inform you on effective methods to age slowly.*

Inner Circle - Intrinsic Aging - The Thread of Life - Genetics, Predispositions

There are some aspects of your epigenetic aging that aren't within your control. Usually these things have to do with your underlying genetic predispositions or the epigenetic traits passed on by your parents and even grandparents. Often times, there is little to do about these factors.

TREATMENT FRAMEWORK

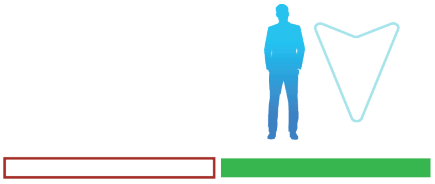
The Impact To You - Where you Stand

Throughout the rest of this report, you will see the graphic below. This will be a quick signal to let you know how your demographic information trends according to the data.

The Red Side: Factors Increasing Your Epigenetic Age

This means that the answers you provided us, and the results we extrapolated from your epigenetic test are associated with higher epigenetic aging. Oftentimes, this is associated with negative health outcomes.

In the paragraphs of text, we will review the impact and the evidence which has been described in the literature so that you can judge the effect of this trend in yourself and how you might be able to address this in your Treatment Framework.



The Green Side: Factors Decreasing Your Epigenetic Age

This means that the answers you provided us, and the results we extrapolated from your epigenetic test are associated with lower epigenetic aging. Oftentimes, this is associated with positive health outcomes.

This is good news! We still encourage you to read the information next to these images. Often, there is a middle ground or "goldilocks zone" with these metrics. This means that some behaviors might be good generally, but bad when done too often. By reading the explanations, or talking to your physician, you can see exactly what activities, history, or actions are beneficial to make efforts to continue this trend!

TREATMENT FRAMEWORK

Genetics

Genetics regulate many of the epigenetic modifications the body has. For instance, the epigenomes of identical twins are known to be more similar than those of fraternal twins [78]. This shows that your own genetic make-up is partly responsible for the way that your body makes methylation changes to itself. Since you can't modify it, it is considered an intrinsic form of epigenetic aging.

Epigenetic Inheritable Changes "The Middle Ground of Nature vs Nurture"

Parental experiences:

Everyone knows that your DNA is 50 percent of each of your parents. But did you know you also inherit some of their experiences?

Experiences of earlier generations can modify regulatory factors affecting gene expression such that the DNA sequence itself is not changed but the individual's physiology and behavior are substantially influenced.[13]

Instinct and predispositions:

An animal mind is not born as an empty canvas: Bottlenose dolphins know how to swim and honey bees know how to dance without ever having learned these skills. Little is known about how animals acquire the instincts that enable such innate behavior. Instincts are widely held to be ancestral to learned behavior but *increasing evidence is showing that these might be epigenetic features passed through the germ line. [5]*

For example, when a mouse has experienced fear of something, changes in DNA methylation and chromatin structure in neurons of the hippocampus help stabilize long-term changes in neural circuits. These changes help the mouse remember what has been learned and support the establishment of new behavioral responses.

Evolutionary changes in epigenetic mechanisms may sculpt a learned behavior into an instinct by decreasing its dependence on external stimuli in favor of an internally regulated program of neural development. There is evidence for such epigenetically driven evolutionary changes in behavior. For example, differences in innate aggression levels between races of honey bees can be attributed to evolutionary changes in brain gene expression that also control the onset of aggressive behavior when threatened. Another example of this intrinsic epigenetic regulation is female puberty. Currently, a few studies support the notion that the activation of neuroendocrine pubertal components is mediated, at least in part, by epigenetic mechanisms. [73]

TREATMENT FRAMEWORK

Epigenetic Age in Utero

You can have age acceleration when you are in the womb. Studies have researched the epigenetic age of children with results showing that every child ages at a difference rate.

Some findings have shown that accelerated epigenetic age when children are in the womb are associated with higher birth weight and birth length and that this difference persisted up to approximately 9 months of age. From age 9 months on wards, these differences continued to attenuate and eventually reversed for weight, resulting in approximately 0.6 kg lower weight at age 10 years per week greater gestational advanced aging. [52]

The amount of touch and coddling you get as a child can affect your aging rate. We know that coddling can affect your age acceleration but implications have not been confirmed. [60]

Did your mother smoke or use nicotine products while she was pregnant with you?

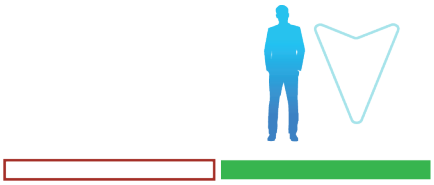
The risk of fast aging in children is about ***3 times higher*** in mothers who smoked versus the risk in nonsmoking mothers.

Did you or your mother have any pregnancy complications?

Prenatal adverse environment is associated with epigenetic age deceleration at birth and hypomethylation at the hypoxia-responsive EP300 gene. P300 gene revealed cg19011939 to be differentially methylated in association with prenatal adversity. This can lead to increased epigenetic age acceleration. [66]

The Impact To You

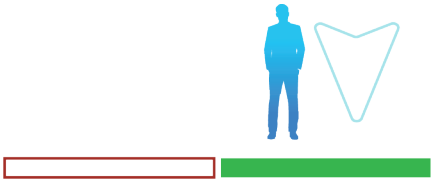
Yes - Unfortunately, if you answered that your mother did smoke or used nicotine products while she was pregnant you. This means you have a ***3 times chance*** of having a higher epigenetic aging rate. However, this is usually only noticeable when you are below 25 years of age!



No - Pregnancy complications is a broad term. However, by the clinical definition, this is linked to increased epigenetic aging. You answered that your mother did NOT have complications while she was pregnant with you. This means that this ***history might have an impact on decreasing your biological age.***

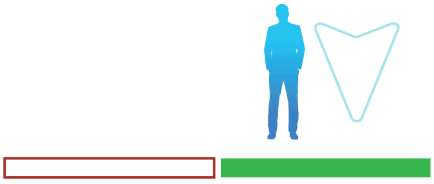
TREATMENT FRAMEWORK

How old was your biological mother when you were born?



Less than 35 - There has been a lot of research linking maternal age to epigenetic changes. You answered that your mother was under 35 years old when you were born. This means that you are ***more likely to have a decelerated aging rate.***

How old was your biological father when you were born?



Less than 40 - To date, there have been no studies done linking parental age to the epigenetic aging rate. However, there have been many studies which document that the older a father is when their child is born, the less longevity benefits are conveyed to their offspring. You answered that your father was under 40 years old when you were born. This is ***most likely a good thing, but it is not conclusive.*** We hope to analyze the data from our test to report just how this metric affects your epigenetic aging rate.

TREATMENT FRAMEWORK

Parental Experiences:

Many studies have linked higher paternal age to reduced benefits in longevity. [82]

Maternal Age:

Unfortunately, maternal age has been documented to be a big influence on several epigenetic changes.

One of the well-described changes occurs in a gene called a carbohydrate N-acetylgalactosamine 4-O sulfotransferase 8 (CHST8). This has some important implications for fertility. CHST8 is predicted to be maternally imprinted and encodes an enzyme necessary for the synthesis of luteinizing hormone (LH).

An LH surge is responsible for triggering ovulation and development of the corpus luteum. This finding may provide additional support for the hypothesis that increased maternal age results in decreased fertility in adult daughters via epigenetic modification of critical target genes.

LHX8 is one of 2 genes which are related to maternal age and obesity as well. In addition to LXH8's key role in reproduction, it is an expression marker for metabolically active brown fat. The other gene linked to brown fat is PRDM16.

Brown fat mass and BMI have been reported to have an inverse association in adults. Meaning the more brown fat you have the lower your BMI.

Additionally, we find an inverse association between maternal age and the adult daughter BMI: This relationship was confirmed in the full Sister Study cohort. The older the mom, the more likely you are to have a higher BMI.

While the associations between maternal age and offspring cardiometabolic health may be modified by many other factors, the biologic underpinning for these relationships may include epigenetic modifications at LHX8 and PRDM16. [61]

TREATMENT FRAMEWORK

Socioeconomics of your parents at birth

Lower SES was associated with higher methylation age for children at birth. SES was negatively and significantly associated with methylation age at birth. [8]

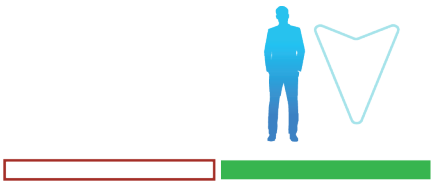
Childhood events:

Did you experience stress as a child such as abuse, financial stress or a parent with a mental illness?

There are times throughout development where we are particularly sensitive to different stimuli. There are several examples of this.

One study found strong evidence of association between advertising exposure and epigenetic aging for sensitive periods during early & middle childhood. This finding aligns with human studies showing the importance of sensitive periods in epigenetic programming [19, 21, 57].

The Impact To You



What level of education does your father have?

Bachelor's degree - You answered that your parents graduated with a degree beyond high school education. This means that your epigenetic age is most likely lower due to this variable. Education level is just correlated and not a treatment to reduce epigenetic age. It is most likely a variable that influences aging rate by stress and other environmental factors.

It seems plausible that the epigenetic age of cells is influenced by environmental inputs in a similar time-susceptible manner. The current findings further emphasize the importance of attending to possible time-dependent effects when studying the effects of adversity on cellular aging, including DNAm and other cellular-based measures of accelerated aging.

The sex-stratified analyses revealed that adversity could differentially affect epigenetic age acceleration in boys and girls. Some of these associations were particularly notable; for example, by age 7.5, girls who were exposed to abuse at age 3.5 were biologically older than their unexposed peers by almost 2 months.

Childhood Abuse [45], financial stress [74], and parental psychopathology [7,45], are all associated with accelerated epigenetic aging in adulthood.

TREATMENT FRAMEWORK

Semi-Centenarians: Anyone over 100 in your family?

It isn't just bad behavior that is passed through gene. Good behavior and results can also be heritable. Semi- supercentenarians (subjects who reached an age of 105-109 years) arguably represent the gold standard of successful human aging because they managed to avoid or postpone the onset of major age-related diseases. If you have had one of these individuals in your family, you are more likely to age much slower.

The offspring of centenarians age more slowly than age matched controls, according to Age Accel and intrinsic age acceleration. [33]

Infectious inheritance

In April of 2020, a study came out showing the first example of an infection epigenetic inheritance in men. This study, from Walter and Eliza Hall Institute in Australia, showed an infection of toxoplasmosis in males can result in epigenetic changes being transmitted to subsequent generations. [79]

Toxoplasma is one of the world's most common parasites, estimated to be carried by between 25 and 80 percent of the global population. Toxoplasma infection can cause an initial mild illness in most people. However, pregnant women, babies, and people with weakened immunity experience severe infections.

The published study documented that Toxoplasma infection in male mice caused changes in levels of 'small RNA' molecules, that were contained in their sperm. This could've potentially altered gene expression in the resulting offspring which could affect development and behavior. Even viral exposure in previous generations could affect your epigenetic age. [79]

The Impact To You

No - You said that you have NOT had someone live over the age of 100 in your family. Since you do not have a grandparent who is a semi-centenarian you are ***less likely to live at a slower rate and live longer.***

TREATMENT FRAMEWORK

The Impact of Sex, Race, and other demographics

What best describes your ancestry/ethnicity?

Race seems to have a significant impact on epigenetics. Although health outcomes in relation to reace are yet to be confirmed/conclusive, current studies have resulted:

Your Selected Ethnicity

European or Caucasian

Unfortunately, all races and ethnicities have not been studied in relation to epigenetic aging. We are hoping to change this! By letting us know, we are able to collect this data and let our computer learning system help us connect the dots between race and aging. While many races have been investigated, we hope to have more substantial data soon!

- Infants from mixed race/ethnicity origin had significantly ***higher methylation age*** and higher ***frequency of fast aging rate*** than that in African-origin black people. [38]

- African Americans have indications of a ***significantly younger immune system*** age than Caucasians after controlling for gender, educational level, diabetes status, and Hypertension. [35]

- According to measures of extrinsic epigenetic age acceleration, Hispanics have a ***significantly older extrinsic epigenetic age*** than Caucasians and ***fewer naïve CD4+ T cells.***

- This pattern of fewer naïve CD4+ T cells is even more ***pronounced for Tsimane,*** who experience ***repeated acute infections*** and elevated, often chronic, inflammatory loads. [35]

- In one famous study, there were three variables linked to extrinsic epigenetic age acceleration: ***race/ethnicity, hypertension, and gender.*** However, this significant association between extrinsic epigenetic age acceleration and hypertension, type II diabetes status is only found in Caucasians, not in African Americans. [35]

- The lower level of intrinsic epigenetic age acceleration in Hispanics echo the finding that Hispanics in the US have a lower overall risk of mortality than Caucasians, despite having a disadvantaged risk profile. The fact that Hispanics have typically had lower intrinsic epigenetic aging but not lower extrinsic epigenetic aging might reflect that Hispanics have higher levels of metabolic/inflammatory risk profiles and have a lower relative CD4+ T cell percentage than Caucasians. [35]

TREATMENT FRAMEWORK

What is your Biological Sex?

Sex morbidity–mortality paradox

The sex morbidity–mortality paradox was first described in the 1970s. It refers to the observation that women have a lower mortality rate compared to men despite being more likely to suffer from other diseases and co-morbid conditions. It has always been assumed that this might be due to behavioral traits such as lifestyle factors or that men might be less likely to go to a doctor in order to be diagnosed with a disease or condition. [44]

However, we still see differences in health after accounting for differences in work-related behavior, smoking, obesity, and other behaviors. This is noted in epigenetic testing.

The Impact To You

Male - As a male, you are more likely to pass away or have other health conditions compared to women. This includes having a ***higher epigenetic aging rate.***

Only one study has really dived into the differences between sexes, noting that epigenetic aging markers show a large and consistent male-biased vulnerability in multiple tissues (blood, brain, and saliva) across all racial groups.

Men have higher IEA and EEA than women even when controlling for education, diabetes, and hypertension. [35]

However, this difference wasn't found in all races. According to the studies evaluation of EEA, Caucasian men are epigenetically older than Caucasian women, but there was not a significant difference in other races such as African Americans or central African populations.

Despite the inclusion of race, it is still clear that some of the processes which lead to advanced epigenetic aging are affecting men more. Additionally, it might have a larger effect on extrinsic aging because men have fewer naïve CD4+ T cells than women in three racial/ethnic groups: Caucasians; Tsimane; and African Americans. [35]

Sex also effects aging of the brain

All tissues have different epigenetic aging rates. However, the impact of sex and tissue aging is still seen in the brain. While sex did not have a significant effect on the epigenetic age of the cerebellum, the study found that other brain regions from men exhibit a significantly higher age acceleration compared to women. [35]

TREATMENT FRAMEWORK

Outer circle - Extrinsic aging

Environmental exposures such as nutrition, disease, stress, activity, medications, and drugs can alter DNA methylation at various stages in your life. These are considered extrinsic factors and are the focus for any health conscious individuals due to their capability of being altered.[2]

TREATMENT FRAMEWORK

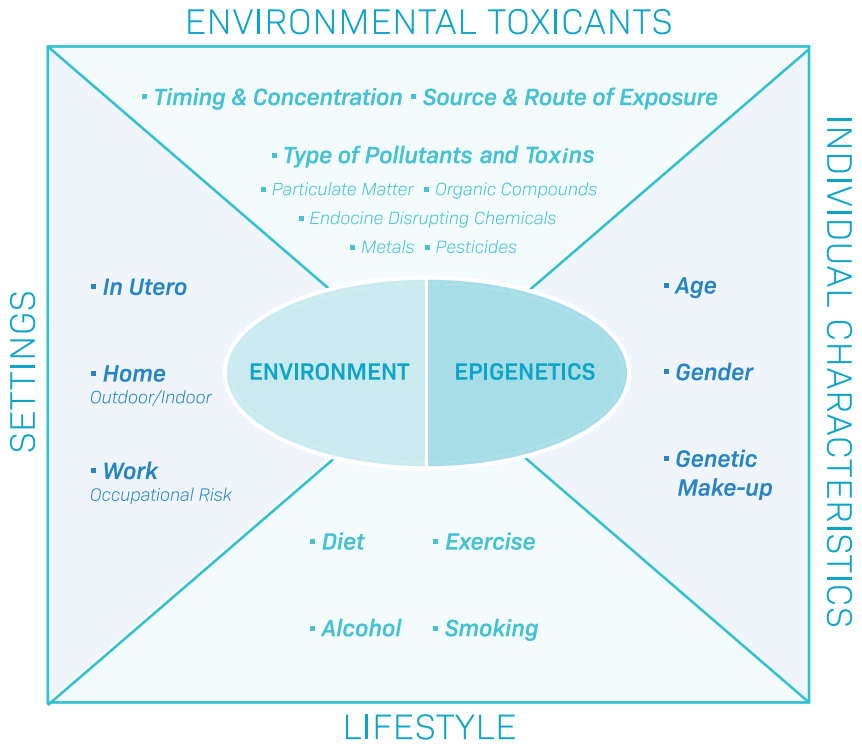
Environmental Exposures

The Trouble with Testing and the Twin Solution:

When setting up a good scientific experiment, one of the most important things to do is to have few variables. By doing this, scientists are able to calculate just how much one independent variable can affect the outcome they are measuring. This is difficult to achieve with the epigenetics of methylation because so much can change this pattern. Therefore, successful studies are completed with large numbers of people and in similar populations.

It is difficult judging what factors in the environment can change an indivdiual's epigenetic aging rate. Even defining what is included in the environment can be difficult. You might consider pollution, but do you account for humidity? One way to solve this is to observe individuals who complete dailiy tasks and activities except for one of two variables. Identical twins share the same DNA and usually share the same environment growing up. It is as close to a controlled experiment as you can get for such a complicated field of research like epigenetics.

In one study looking at two popular clocks, they estimated that 40 percent of the determination of the aging rate was due to the factors you can't control like your DNA or the influences and lives of your parents. However, this means that 60 percent is changeable. This means you're able to greatly alter your own aging.



Correlations to Toxic Exposures

Oftentimes, methylation epigenetics doesn't have enough data yet to be a stand alone diagnostic. However, we are able to help narrow down the scope of diagnosis by looking at the correlated changes of the DNA methylation to different types of diseases or exposures.

Environmental exposures are a good example of this. Below is a list of some environmental toxins which can help shape the epigenome. If you are concerned you have been exposed to these toxins, please let us know. We will work to read your DNA and let you know the likelihood of exposure. [56]

Exposures	Global Methylation	Gene-Specific Methylation	Exposure-Associated Health Impact
Aflatoxin B1	Hypomethylation associated with exposure	71 CpG sites associated with prenatal exposure	Hepatocellular carcinomas, reduced growth, immune deficiencies
Air pollution	Hypomethylation typically associated with exposure in adults, prenatal exposure is associated with both hypo- and hypermethylation	MAPK pathway members, ACE, iNOS, ICAM-1, TLR2, IL-6, TET1	Accelerated lung aging, loss of lung capacity, asthma, bronchitis, emphysema, and cancer
Arsenic	Hypomethylation associated with exposure with sex-specific directionality shown as well	KCNQ1, SQSTM1, sex-specific profilese	Lung cancer conditions and diabetes in adults; prenatal exposure is associated with increased incidence of infection, neurocognitive effects, and increased neonatal mortality
Bisphenol A	Hypomethylation associated with exposure in females, potential nonmonotonic dose responses	SNORD, SULT2A1, COMT	Neurocognitive effects, increased incidence of cancer, and heart conditions from prenatal exposure
Cadmium	Hypomethylation associated with exposure	DNMT1	Cancer, lung, bone, and kidney disease, developmental toxicity
Chromium	Hypomethylation associated with exposure	Not assessed at present	Cancer
Lead	Not assessed at present	Alterations in imprinted genes, sex-specific response	Neurotoxicity, developmental toxicity
Mercury	Not assessed at present	EMID2, sex-specific profiles	Neurotoxicity
Polycyclic Aromatic Hydrocarbons	Hypomethylation associated with exposure	HIN1, ESR1, TWIST1	Cancer
Persistent Organic Pollutants	Nonmonotonic association with exposure	IGF2, TNF-α, NR3C1	Various health effects
Tobacco Smoke	Hypomethylation associated with exposure	AHRR, CNTNAP2, MYO1G	Cancer, developmental toxicity, cardiovascular disease, chronic respiratory conditions
Nutritional Factors	Hypermethylation associated with exposure	IGF2, RXR-α, PLAG1	Proper development
Non Chemical Stressors	Not assessed at present		Various health effects

TREATMENT FRAMEWORK

Air Pollutants

Due to environmental changes and increased activity, the air is becoming more polluted. To objectively measure the amount of pollution in the air scientists have created a term called PM2.5. PM2.5 refers to atmospheric particulate matter (PM) that have a diameter of less than 2.5 micrometers, which is about 3 percent the diameter of a human hair.

Particles in this category are so small that they can only be seen with a microscope and tend to stay longer in the air than heavier particles. This increases the chances of humans and animals inhaling them into their bodies. Dueto their minute size, particles smaller than 2.5 micrometers are able to bypass the nose and throat and penetrate deep into the lungs, possibly entering the circulatory system.

Studies have found a close link between exposure to fine particles and premature death from heart and lung disease. Fine particles are also known to trigger or worsen chronic disease such as asthma, heart attack, bronchitis and other respiratory problems.

A study published in the Journal of American Medicine suggests that long-term exposure to PM2.5 may lead to plaque deposits in arteries, causing vascular inflammation and a hardening of the arteries, which can eventually lead to heart attack and stroke. Scientists in the study estimated that for every 10 micrograms per cubic meter (µg/m3) increase in fine particulate air pollution, there is an associated 4%, 6% and 8% increased risk of all-cause, cardiopulmonary and lung cancer mortality, respectively. [17]

In addition to those health effects, we also see changes in the epigenome and in the epigenetic age rate.

In a study with almost 600 men from the Northeastern USA enrolled in the Normative Aging Study (NAS), a 1 µg/m3 increase in one-year PM2.5 exposure was significantly associated with a 6-month increase in their epigenetic age. [63] In a similar study using 1,777 German participants of the Cooperative Health Research in the Region of Augsburg (KORA) study, a 0.97 µg/m3 increase in long-term exposure to PM2.5 was associated with a 0.33-year increase in extrinsic epigenetic age acceleration. [16] In addition to PM2.5 mass, associations with a particular clock have been observed with specific PM2.5 components such as ammonium and sulfate. [16]

Pollution and particles are negative factors for your aging and wearing a mask while traveling is a possible intervention. Due to pollution's specific effect on extrinsic epigenetic aging, there is a possible association with decreased immune functioning.

TREATMENT FRAMEWORK

Metal and Pesticide Exposures

Two studies have examined associations between metal exposures and epigenetic aging to date.

A study of urinary cadmium in 40 non-smoking women from Thailand and a study of blood cobalt and chromium levels resulting from chronic exposure due to metal on metal hip replacements found no associations between any of the metals examined and Epigenetic age. In Thailand, 40 non-smoking women completed a study of urinary cadmium as well as blood cobalt and chromium levels. This was to result chronic exposure due to metal-on-metal hip replacements. However, no associations were found between betal examined and epiage, concluding metal exposure does not affect epiage. [76]

A study observed three organochlorine pesticides – (4-chlorophenyl)-1,1-dichloroethene (DDE), hexa-chlorobenzene (HCB), and trans nonachlor (TNC) – in the plasma of 967 Swedish individuals. All three exposures were positively associated w ith larger differences between chronological and epigenetic

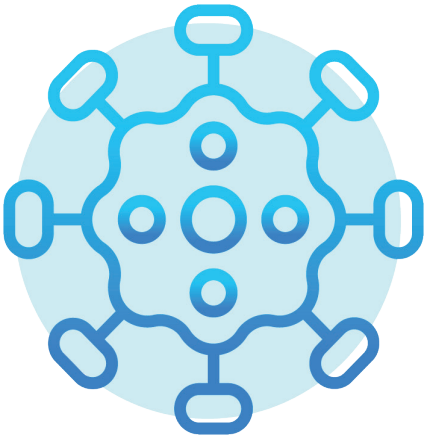
TREATMENT FRAMEWORK

Infectious Exposures

As mentioned earlier with toxoplasmosis, viruses can have an effect on epigenetics. However, how do some common viruses affect epigenetic aging?

Of all of the infectious agents studied for their relationship with epigenetic age, Human Immunodeficiency Virus (HIV) is the most widely examined.

In one study HIV positive individuals were found to have brain and blood samples that were 7.4-years and 5.2-years higher, respectively, compared to controls.



That the load of the virus was associated with higher aging rates. Adult male cases with a detectable viral load (>35 HIV copies/mL) had a 3.6-year higher methylation age as compared to adult male cases with an undetectable viral load. [32]

In addition to HIV, *H.Pylori* (an abnormal bacteria from the gut), and cytomegalovirus (CMV) have both been linked to changes in epigenetic aging. [80]

In a study of 1509 German adults who had documented *H. pylori* infections, were all associated with increases in epigenetic methylation age of 0.4, 0.6. and 1-year, respectively and independent of white blood cell distributions. [16] In peripheral blood cells from 122 nonagenarians (a person who is from 90 to 99 years old) and 21 young healthy controls from a sub-cohort of the Finland Vitality 90+ study, ***epigenetic methylation age was 2.5-years higher in CMV positive individuals versus those without disease.*** [41]

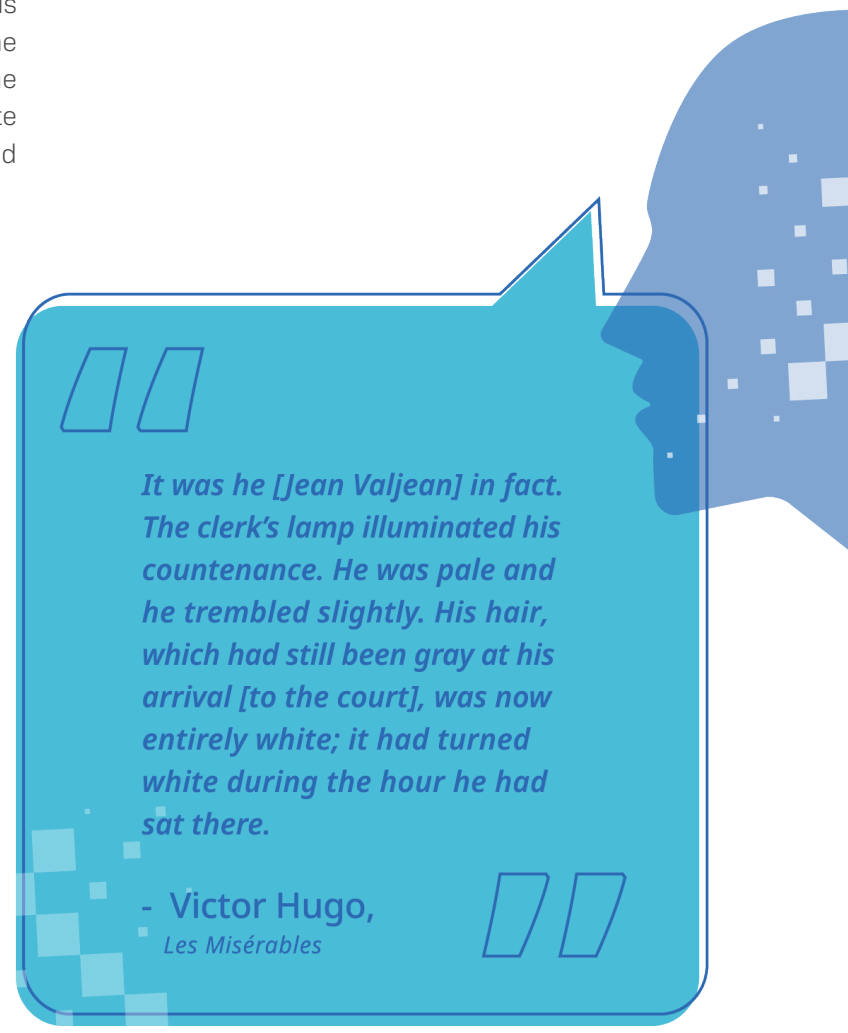
Alterations in blood cell compostion may play an important role, yet, the underlying mechanisms connecting infections and DNAm-age have yet to be elucidated. Other mechanisms are needed to explain associations in non-blood tissues, even for those that seems to be independent of assessed blood cell proportions.

TREATMENT FRAMEWORK

Psychosocial Exposures

Psychosocial exposures such as stress, adversity, and socioeconomic status, may also impact epigenetic aging.

In Hugo's fictional work Les Misérables, an extreme stressor causes the main character, Jean Valjean, to undergo accelerated aging, depicted as rapid whitening of his hair. This dramatic depiction is just one among innumerable examples—found in literary works, movies, and folklore legends—of individuals whose "biological clocks" appear to tick fast in the face of life adversity. Beyond fiction, however, the connection between psychosocial stress and rate of biological aging is also seen in everyday life and clinical practice.



TREATMENT FRAMEWORK

Adrenal Stress and Fatigue

Rate your Lifetime stress 1-10?

An important risk factor for accelerated aging and aging-related diseases is psychological stress. Although stressors are ubiquitous in nature and necessary for survival, excessive and chronic stress has been associated with accelerated cellular aging as well as increased risk for aging-related disease phenotypes, including cardiovascular disease, immune dysregulation, and late-life neuropsychiatric disorders. Furthermore, stressors occurring during sensitive developmental periods, such as childhood maltreatment, have been linked with later development of aging-related diseases. Lastly, stress-related psychiatric disorders, including major depression and post-traumatic stress disorder (PTSD), are themselves risk factors for such diseases.

The Impact To You

We didn't get a response from you on this question so we are unsure of how this variable might correlate to your aging rate.

In a 2015 study by Zannas et al, the authors showed that cumulative lifetime stress may accelerate epigenetic aging. They also hypothesized that these effects could be driven by glucocorticoid-induced (cortisol) epigenetic changes. Cortisol is the hormone that is upregulated during stress and can cause people to put on weight. [84]

Glucocorticoids, a class of endocrine signaling hormones which includes cortisol, are a component of the biological response to stress. ***85 of the 353 loci that comprise the epigenetic clock are located near glucocorticoid receptor elements, and 110 loci showed altered DNA methylation after exposure to dexamethasone, a glucocorticoid receptor agonist.*** [84]

Researchers have proposed biological mechanisms that may connect stress to epigenetic alterations and DNA methylation age/aging in particular. Accordingly, stress-inducing psychosocial exposures are frequently associated with epigenetic age.

Limiting stress and this hormone might be a good way to avoid advanced epigenetic aging.

TREATMENT FRAMEWORK

Stress, Trauma, & Post-traumatic Stress Disorder (PTSD)

In a study of 392 adults recruited from urban hospitals, the relationship of life stress was associated with higher epigenetic age, an observation which was more prominent in older participants and those who experienced minimal childhood mistreatment. In this particular study, however, epigenetic age was not related to childhood trauma, current stress, depressive symptoms or PTSD symptoms.

Combat-related trauma and PTSD have been associated with increased epigenetic age in a few studies of veterans. In veterans of the Iraq and Afghanistan conflicts (N = 281) lifetime PTSD was related to increased epigenetic age.

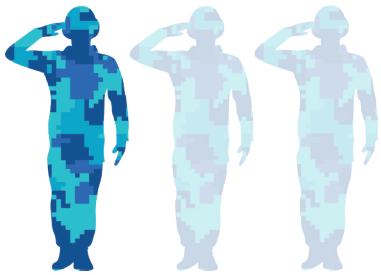
In 339 middle-aged, trauma-exposed veterans, hyperarousal PTSD symptoms were associated with increased epigenetic age. [84]

In a longitudinal study, epigenetic age was determined in 96 Dutch military personnel deployed to Afghanistan, from blood draws conducted before and 6 months post-deployment. ***Combat-related trauma was significantly associated with an increase in epigenetic age of about 2 years over the course of deployment.***

A meta-analysis of 9 cohorts (n = 2186, civilian and military) found modest associations of accelerated epigenetic age with exposure to child trauma, and with lifetime PTSD severity. [15]

22%
of veterans suffer from PTSD or depression

34%
of veterans suffer from other mental concerns



1 OUT OF 3
veterans seek help

TREATMENT FRAMEWORK

Childhood Adversity and Trauma

Studies of childhood and adolescent adversity have been the first to use biological epigenetic aging as a potential measure of intervention efficacy, or effect modification by intervenable factors.

Using 399 parent and child pairs from rural Georgia, USA, one study aimed to assess if parental depressive symptoms at child age 11 forecast epigenetic age at child age 20, as well as the potential of an intervention program, the Strong African American Families program (SAAF), which aimed to improve supportive parenting and family relationships.

Among the control group, elevated parental depressive symptoms were associated with future increased epigenetic age in children, but the association was abolished in those receiving the SAAF intervention. Similarly, a longitudinal study of 616 African American youths (16–17 years old at recruitment) in rural Georgia found an ameliorating effect of a supportive family environment on the relationship of epigenetic age to experience of racism. ***Among the youth with a less supportive family exposure and higher levels of racial discrimination during early adulthood was associated with higher epigenetic age.*** [16]

In a separate study of 101 children (age 6–13 years) from a primarily low income, highly traumatized neighborhood populations in Atlanta, Georgia, direct experience of violence was significantly associated with increased epigenetic aging. There was a suggestive ($p < 0.10$) association between witnessing violence and epigenetic aging. [16]

Associations of childhood adversity and trauma with biological age measures appear consistently adverse, unless moderated by an ameliorative co-exposure, whether preexisting or the product of intervention.

TREATMENT FRAMEWORK

Socioeconomic Status and Hardship

Notable studies have identified associations between SES and epiaging. Using a meta-analysis of cohort specific associations, low SES was associated with a 0.99-year greater epigenetic aging rate when comparing the highest to lowest SES categories. [25]

The trajectory of a socioeconomic life course has consistent effects on epigenetic age.

Two studies of epigenetic age were conducted on African-American adolescents residing in rural Georgia and examined the direct or modifying impact of economic hardship on epigenetic age using samples collected around the Great Recession.

One study examined the impact of economic hardship during the 2007–10 economic recession on epigenetic age in 330 African American adolescents (mean age 16.6 years in 2007). ***Adolescents exhibited a mean 1.42-year increase in epigenetic age with each as categorical measures of economic adversity increased.*** These findings are mirrored in observations of increased allostatic load and decreased self-reported overall health with increased epigenetic age. [10]

A second study noted that while self-control was associated with several favorable psychological outcomes (e.g., lower rates of depressive symptoms, substance use, and aggressive behavior), among low SES youths better self-control was associated with an increased biological age of 2.27-years. In contrast, among less-disadvantaged subjects, better self-control was associated with a 2.14-year deceleration. [16]

TREATMENT FRAMEWORK

Do you have Allergies and Asthma?

"We know that the prevalence of allergies and asthma has been increasing over the past decade. The genome hasn't changed, but some of the ways that the environment is interacting with our genomes may have. - Dawn DeNeo, MD, MPH"

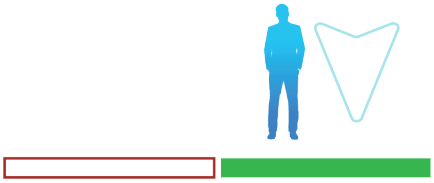
At mid-childhood (mean age, 7.8 years) in Project Viva, epigenetic age and age acceleration were cross-sectionally associated with greater total serum IgE levels and greater odds of atopic sensitization.

Every 1-year increase in intrinsic epigenetic age acceleration was associated with a 1.22, 1.17, and 1.29 greater odds of atopic sensitization and environmental and food allergen sensitization. [70]

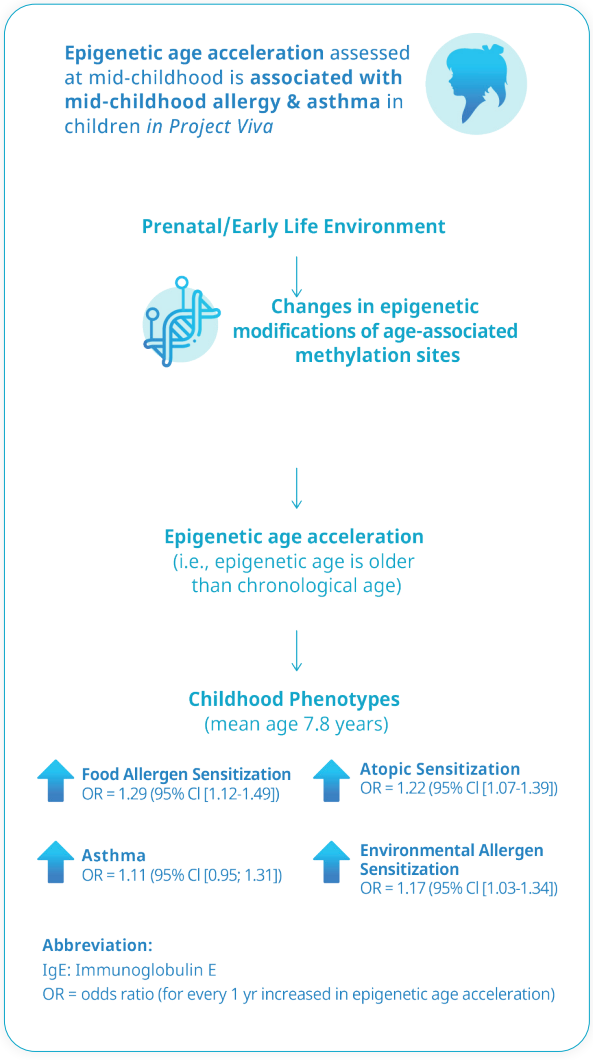
Extrinsic epigenetic age acceleration was also cross-sectionally associated with current asthma at mid-childhood. Biological age and age acceleration at birth and early childhood were not associated with mid-childhood allergy or asthma.

Because the epigenetic clock might reflect immune and developmental components of biological aging, the Project Viva study suggests pathways through which molecular epigenetic mechanisms of immunity, development, and maturation can interact along the age axis and associate with childhood allergy and asthma by mid-childhood. [70]

The Impact To You



No - Epigenetic age acceleration is associated with allergies and asthma. Because you answered that you do not have asthma, you are more likely to have a lower epigenetic aging rate.



TREATMENT FRAMEWORK

Education Level:

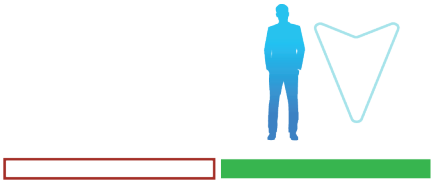
Higher education has been a demographic variable that has been linked to many positive health outcomes including reductions in morbidity and mortality risk.

How is it correlated to Epigenetic aging?

It seems that it has a significant effect on the extrinsic epigenetic aging rate of a person, according to a 2017 study. *In this study it was correlated that those with more education have less advanced aging.* It is not conclusive that receiving an education reduces epigenetic age, there is ony a correlation with the population studied.

This study also looks into fitness and nutrition which we will be discussed later. [72]

The Impact To You



Master Degree - You answered that you graduated with a degree beyond high school education. This means that your epigenetic age is most likely lower due to this variable. Education level is just correlated and not a treatment to reduce epigenetic age. It is most likely a variable that influences aging rate by stress and other environmental factors.

Nutrition

There are many differing opinions out there about what is the best diet. Some focus on macronutrients such as carb intake, while others focus on the timing of meals. However, epigenetic testing gives us an objective metric to look at how some diets and supplements can affect the aging process.

The Mediterranean Diet

The Mediterranean diet, which is considered by UNESCO as a heritage of humanity, is a well-balanced mix of nutrients, antioxidants, and anti-inflammatory molecules. This diet has demonstrated favorable effects on cardiovascular risk, blood pressure, cancer, inflammation, and frailty status. It has been observed that it can impact methylation of inflammation-related genes in peripheral blood cells.

The role of the Mediterranean diet in promoting healthy aging has been recently investigated in a new European project: New dietary strategies addressing the specific needs of elderly population for an healthy aging in Europe (NU-AGE). The aim of the NU-AGE project is to investigate how an intervention based on the Mediterranean diet, specifically tailored according to the nutritional needs of people over 65 years of age, can impact on age-related diseases and functional decline, possibly modulating inflammation and its outcomes.

At baseline and after the 1-year intervention, results achieved so far in the framework of this study have demonstrated a beneficial effect of the Mediterranean-like diet on global cognition and episodic memory, osteoporosis, immune function, and cardiovascular health, as well as on the proteasomal proteolysis.

There still remains little evidence on the biomarkers associated with the Mediterranean diet. However, one study looked at the effect of 100+ participants and the effect of their epigenetic aging.

Their study observed a trend towards the epigenetic rejuvenation of participants after the nutritional intervention. The effect was statistically significant in the group of Polish females and in subjects who were epigenetically older at baseline.

Together, these findings suggest that the Mediterranean diet can promote epigenetic rejuvenation but with country-, sex-, and individual-specific effects, thus highlighting the need for a personalized approach to nutritional interventions. [30]

TREATMENT FRAMEWORK

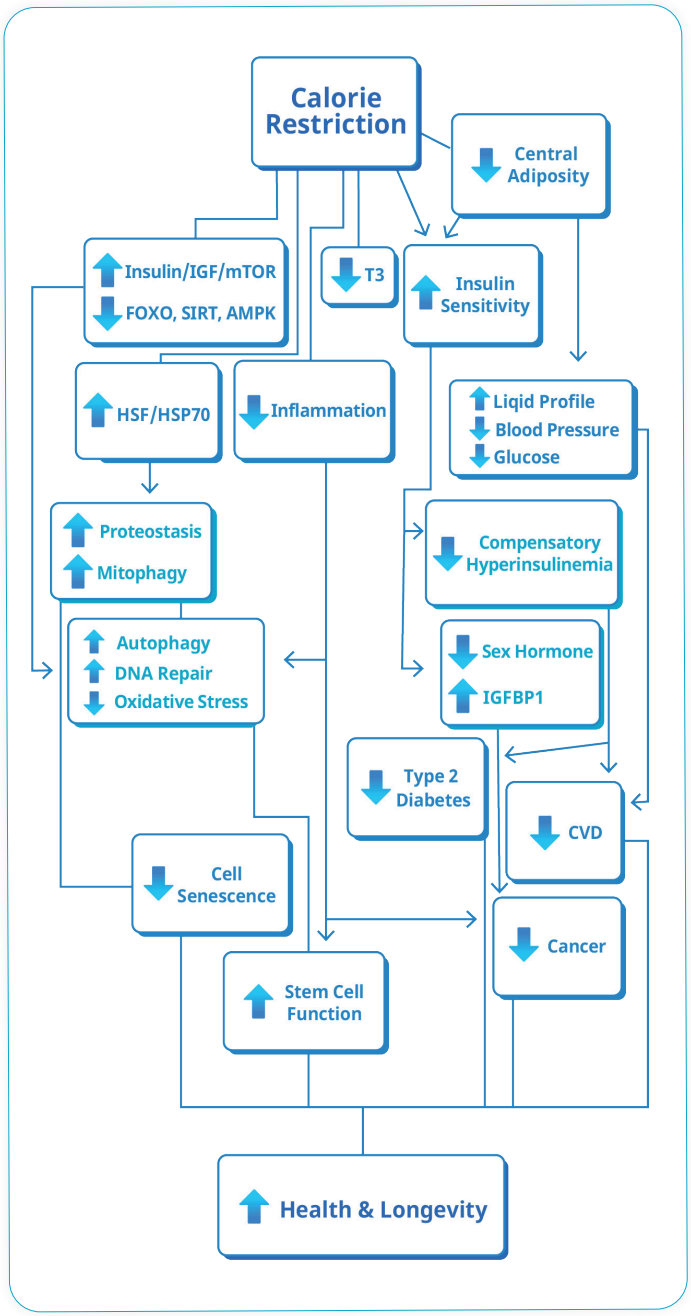
Calorie Restriction

Calorie restriction (CR) without malnutrition is the most studied, robust, non-genetic, non-pharmacological, and experimental intervention for extending healthspan and lifespan in multiple animal models.

In budding yeast, fruit flies, and worms, CR can dramatically extend lifespan (2–3 fold). [77] ***A 20 to 50% reduction in caloric intake, without malnutrition, in some strains of rats and mice prolongs median and maximal lifespan up to 50%. This prevents or delays the onset of many chronic diseases, such as obesity, type 2 diabetes, cancer, nephropathy, cardiomyopathy, neurodegeneration, and multiple autoimmune diseases.*** [62]

Hundreds of preclinical studies have shown that dietary restriction, inhibited by key nutrient-sensing and inflammatory pathways, activates multiple molecular pathways that promote proteostasis, genome stability, stress resistance, and stem cell function. Data collected in non-human primates indicate that calorie restriction in combination with diet quality modifications markedly decreases the incidence of cardiovascular disease, cancer, diabetes, and attenuates age-related neurodegeneration, sarcopenia, and auditory loss.

Finally, data from human studies show that calorie restriction remains the cornerstone in the prevention and treatment of obesity and its complications. Moderate CR achieved through intermittent fasting or restricting feeding in combination with regular physical activity most likely exerts additional beneficial health effects even in non-obese individuals. However, a general facet of modern life in the developed world is the near-constant availability of food. So some researchers have developed some diets to mimic fasting or calorie restriction. [62]



TREATMENT FRAMEWORK

Dr. Valter Longo's Fasting Mimicking Diet

One of the most popular calorie-restricting diets is the Fasting Mimicking Diet (FMD) popularized by Dr. Valter Longo. The longevity diet Dr. Valter Longo developed consists of two parts: the "fasting" phase and the "whole foods" phase. The fasting phase isn't necessarily complete fasting. Rather, it involves consuming a series of packaged herbal teas, soup blends, energy bars, oils, and drinks.

They are to be rationed over the course of five days. After those five days, the dieter can go on to the whole foods phase. During the whole foods phase, the dieter can go back to eating "normal" food that they can get at the grocery store. They do have to make healthy eating choices, though, or all the space freed up during the fasting phase will be put to waste. There's a wealth of research on how intermittent fasting might help with longevity and youthfulness. Intermittent fasting, they say, can reset our bodies and our genes. [50]

While there is not yet a trial published on this at the moment, there is a highly popularized anecdotal trial on this by the radiant Gwenyth Paltrow and her company, Goop Lab. Here, Gwenyth and two of her team members test whether different diets can make your body younger, and therefore healthier, by reducing their epigenetic age. Gwenyth, 46 years old at the time of filming, was prescribed the most extreme of the test diets, the fasting mimicking diet. Following this five-day cleanse, her biological age was 44.2. Goop's chief content officer, Elise Loehnen, 40 years old, was put on a three-week Mediterranean-style diet. Her biological age was 37.9 after the pescatarian, mostly plant-based diet. Wendy Lauria, Goop's vice president of marketing, 49.5 years old, was assigned a three-week vegan diet of plant-based meals, excluding all animal products like meat, fish, milk, and eggs. Lauria had a biological age of 48.4 after her given diet.

In conclusion, Gwenyth came out on top in the final test results, which showed that her fast-mimicking regimen shaved 1.7 years off her biological age, bringing her to a youthful 42.5 (compared with her actual age of 46 years). The results of her experiment have been backed up by some data from mouse clinical trials. A 2017 study from the Max Planck Institute for Biology of Ageing looked at dietary restriction in mice and its effect on genome wide methylation. While they didn't directly address epigenetic age, they found that dietary restriction is generally strongly protective against age-related changes in DNA methylation. During aging with dietary restriction, DNA methylation becomes targeted to gene bodies and is associated with reduced gene expression, particularly of genes involved in lipid metabolism.

Overall their results revealed that dietary restriction remodels genome-wide patterns of DNA methylation so that age-related changes are profoundly delayed, while changes at loci involved in lipid metabolism affect gene expression and the resulting lipid profile. [31]

TREATMENT FRAMEWORK

Bioactive Compounds and Longevity

Although calorie restriction has been shown to have a beneficial role in aging, calorie restriction therapy has several limitations or potential side effects, such as infertility, menstrual irregularities, hypertension, and depression. Therefore, recent studies have aimed to identify bioactive compounds that may mimic caloric restriction and provide therapeutic anti-aging effects.

Direct evidence shows the linkage between bioactive compound consumption and longevity is scarce. However, several studies have reported beneficial effects of natural compounds on age-related phenomena, mainly in providing anticancer and anti-inflammatory effects. [31]

TREATMENT FRAMEWORK

Resveratrol

Resveratrol is the most characterized bioactive polyphenolic compound in anti-aging diets. Dietary polyphenols have antioxidant capacity and protect against age-related degenerative diseases. They can activate endogenous defense systems and modulate cellular signaling processes. Resveratrol is found in grapes, grape-based red wine, as well as strawberries and blueberries. [67]

The possible role of resveratrol in extending the life span recently gained worldwide attention. Resveratrol has been identified as a potent SIRT1 activator that mimics the effects of caloric restriction and regulates longevity from lower organisms to humans. In 2003, Howitz and colleagues showed that resveratrol increases the deacetylase activity of SIRT. A number of studies showed that resveratrol induced SIRT1 activity in several species. Resveratrol mimics caloric restriction effects, which may result in an increased life span.

Although the effects of resveratrol and SIRT1 on longevity are still debated, resveratrol clearly appears to improve metabolism and attenuate the risk of age-related chronic diseases in animal models. For example, increased SIRT1 activation from resveratrol improves energy expenditure and prevents diet-induced obesity and other metabolic diseases. [36]

In addition, middle-aged mice on a high-calorie diet that were treated with resveratrol showed health and longevity benefits. In humans, resveratrol supplementation induces metabolic changes in obese humans, mimicking the effects of caloric restriction. In addition to metabolic regulation, resveratrol has an intrinsic antioxidant capacity and induces the expression of antioxidant enzymes, which reduces oxidative stress. To date, little is known about the underlying epigenetic mechanism by which resveratrol improves longevity and aging-related metabolism. Research suggests that resveratrol may target metabolism-related pathways, such as AMP-activated protein kinase and peroxisome proliferator-activated receptor-gamma coactivator 1 a. [6]

In addition to resveratrol, you may see other research on several bioactive components of which beneficial effects are mediated by epigenetic modifications, namely: sulforaphane, epigallocatechin-3-gallate (EGCG), quercetin, and genistein. All of these have been highlighted for their epigenetic effect on aging. [69]

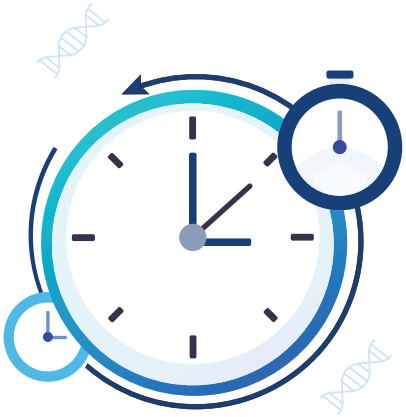
TREATMENT FRAMEWORK

Eating Fish and Chicken

In the same study that looked at the dietary effects of alcohol, the consumption of fish and chicken affected epigenetic aging was analyzed. Those who had fish more frequently were less likely to have a higher extrinsic epigenetic age acceleration. This is consistent with prospective studies suggesting that fish consumption is protective against various age-related diseases. The benefits of fish intake may be mediated in part through the omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which stimulate the synthesis of anti-inflammatory cytokines. ***This was further supported by the authors' findings that CRP—a well-known marker of inflammation—was the most significant explanatory biomarker of extrinsic epigenetic age acceleration.***

Higher fish consumption may lower extrinsic epigenetic age acceleration due to beneficial anti-inflammatory or metabolic effects.

Similarly, the same study found that poultry consumption was associated with a decreased intrinsic age rate and lower BMI after adjusting for potential confounders. [72]



Extrinsic Epigenetic Age	Intrinsic Epigenetic Age
↓ Fish	↓ Poultry
↓ Fruits & Veggies	↓ HDL Cholesterol
↓ Moderate Alcohol	↑ Insulin & Glucose
↓ Edication & Income	↑ C-Reactive Protein
↓ Exercise	↑ BMI & Waist-to-Hip Ratio
↓ HDL Cholesterol	↑ Triglycerides
↑ Insulin & Glucose	↑ Systolic Blood Pressure
↑ C-Reactive Protein	
↑ BMI & Waist-to-Hip Ratio	
↑ Triglycerides	
↑ Systolic Blood Pressure	

Blue Arrow: Decreases Epigenetic Age
Red Arrow: Increases Epigenetic Age

TREATMENT FRAMEWORK

Alcohol

While many might instinctively think that alcohol might accelerate epigenetic aging, one study conducted on this actually showed the opposite.

Alcohol consumption was negatively associated with extrinsic epigenetic age acceleration despite adjusting for potential confounders such as socioeconomic status. This is consistent with prospective studies which have identified light to moderate alcohol intake as a protective factor against all-cause and CHD-related mortality. It is supported by a recent publication that found an inverse association between epigenetic age and alcohol intake in Caucasian and African American individuals.

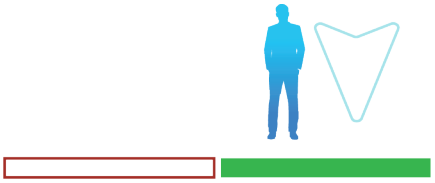
In a study from UCLA, researchers found that one monthly drink had a positive effect. It remained consistent when adding weekly and daily intake levels as well.

The association appears to be driven by wine consumption though there is also a trend towards association with beer. This is consistent with other studies that have suggested that wine may have added benefits compared to light alcohol consumption.

It has been postulated that this may also be related to the anti-inflammatory effects of light alcohol consumption, which are associated with decreased circulating levels of inflammatory markers such as IL-6 and CRP. [72]

Alternatively, this may be the result of reverse causation, whereby those with health issues abstain from alcohol consumption due to their illness, however, other interventional studies support a protective effect of moderate alcohol consumption.

Do not change drinking habits without talking to your physician.



3-5 times per week - You answered that you drink with relative frequency. It is no surprise that high alcohol consumption is correlated to negative health effects. However, in moderation (including no binge drinking), it looks like alcohol has a correlation to reduced epigenetic aging. This means 1 drink per month or week might have a positive effect.

Tobacco

Tobacco smoking is a major public health problem, associated with substantial preventable morbidity globally. Active smoking in adults accounts for a large proportion of age-related diseases, including various forms of cancer, respiratory, and cardiovascular diseases. Recent studies have demonstrated the role of DNA methylation, one of the main forms of epigenetic modification, in the pathways of smoking and smoking-induced diseases via regulating gene expression and genome stability.

An increasing number of smoking-related CpG sites in various genes, such as *AHRR, F2RL3, and GPR15,* have been discovered by epigenome-wide association studies (EWASs) based on whole blood samples. This has been shown to be useful as qua ntitative biomarkers of current and past smoking exposure as well as predictors of smoking-associated health risks. This creates potential for future testing that quantifies the amount smoked throughout one's life

Do you smoke?

None - ***Despite many changes in the epigenome, smoking isn't necessarily correlated to increased epigenetic age which highlights that not every poor lifestyle choice is associated with an increased epigenetic aging effect in blood tissue.*** *[29]*

Illicit Drugs

Although studies on illicit drugs are minimal, it is a growing area of focus with many studies in development.

TREATMENT FRAMEWORK

Pregnancy

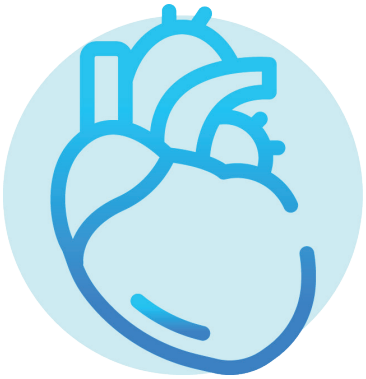
Have you been pregnant?

Pregnancy also affects aging. One study suggests that Pregnancy (gravidity) predicts shorter telomeres and epigenetic age acceleration, measures of mitotic and non-mitotic aging, among young women.

This supports other data showing the cost of reproduction from pregnancy in humans as it relates to age. [75]

TREATMENT FRAMEWORK

Diseases



CHD

DNA methylation is associated with the risk of developing coronary heart disease (CHD), uses methylation levels at 52 CpG sites. CHD events include: unstable angina, heart attack, cor nary revascularization, and coronary death.

Your race/ethnicity, chronological age, and sex are related to your susceptibility to developing CHD. Biomarkers of epigenetic aging can address the mortality rates of CHD and how epigenetic rates of aging are found to be significantly associated with race, sex, and chronological age.

In the first-ever study to use epigenetic measures as an estimate for aging rates amongst gender and ethnic groups, differential mortality rates across these groups were noted. The study used thousands of participants across these ethnic groups: 1387 African ancestry, 2932 caucasian, 657 Hispanic, 127 east Asians, and 59 Tsimane Amerindians.

Findings show that women have lower rates of mortality than men despite having higher rates of morbidity. Hispanics and Tsimane have lower intrinsic epigenetic age acceleration (IEAA) and longer life expectancies but higher extrinsic epigenetic aging rates than Caucasians. African Americans have lower extrinsic epigenetic age acceleration (EEA) than Caucasians and Hispanics.

Notably IEAA is not associated with CHD risk factors, but EEAA was positively correlated with CHD risk factors like triglyceride and creatinine levels. [35]

Large-scale studies show that risk factors for CHD include smoking, obesity, hypertension, serum lipids, and type-2 diabetes. These are all linked to differences in leukocyte DNA methylation. The largest longitudinal study of its kind. with 11,461 participants, found pathways to CHD, including calcium regulation, kidney function, and gene regulation mechanisms that involve non-coding RNAs.

Associations between leukocyte DNA methylation and risk of CHD are clinically relevant. These associations have the potential to present novel avenues for targeting disease pathways and developing therapeutic interventions. Several of the 52 CHD associated CpG sites map genes with roles in calcium regulation and kidney function. [1]

TREATMENT FRAMEWORK

Down Syndrome

Individuals with the genetic disorder, Down syndrome, have an increased risk of having chronic diseases that are associated with older age. The disorder is interpreted as segmental progeria affecting at least two different tissues and is characterized by rapid aging starting in early childhood.

Not only is this an intellectual disability but it is also linked to the clinical manifestations of rapid aging. Trisomy 21 is linked to the acceleration of the biological age of tissues and significantly increases the ages of blood and brain tissue.

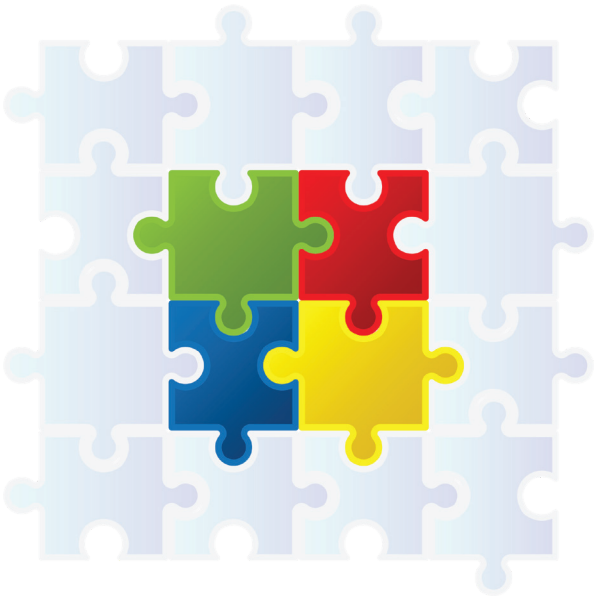
A method that predicts adults with Down syndrome's biological age is based on DNA methylation at 353 CpG sites. These sites are strong indicators for these individuals' biological age. Using CpGs associated with Down syndrome status and age acceleration helps determine the specific set of conditions associated with accelerated aging.

The early onset of epigenetic changes is linked to Down syndrome pathologies which include: premature wrinkling, greying of hair, hypogonadism, early menopause, hypothyroidism, declining immune function, and Alzheimer's disease. [34]

TREATMENT FRAMEWORK

Autism

The prevalence of autism spectrum disorder has been increasing over the past 20 years. Autism spectrum disorder is a clinical grouping of neurodevelopmental disorders characterized by debilitated social communication and repetitive behaviors. Many children and adults diagnosed with autism have comorbid health problems and are three to ten times more likely to die prematurely. The biological makeup of people with autism spectrum disorder is linked to other illnesses such as epilepsy, gastrointestinal, and respiratory disorders. [68]



"Comorbidity is to be expected in autism spectrum disorders- directly or indirectly. Comorbid conditions may be markers for underlying pathophysiology and request a more varied treatment approach."

-Jorn Isaksen et al., 2012 *'Children with autism spectrum disorders: The importance of medical investigations.'*

Genetic discoveries of autism spectrum disorder provide evidence of a strong inherent component for several cases of affected individuals. Genetic risk for autism spectrum disorder lie in several genes but will likely reside in immune-related genes. however, this is not only depended on genetic inheritance.

Impairments of microglial function explain the mechanisms that react to environmental influences on the developing brain's DNA methylation. Individuals with autism spectrum disorders exhibit age-related changes in the trajectory of microglial and synaptic function, suggesting a genetic risk for autism which influences regional cortical gene expression.

Epigenetic dysregulation of synaptic genes at the transcriptional level contributes to autism susceptibility. Abnormal epigenetic modifications, known as epimutations in DNA, can be acquired throughout life. Impaired methylation is evident in environmental factors' role in autism risk. High levels of impaired methylation are common in people affected by autism compared to other groups and it has a pathological role in the development of autism spectrum disorder. [58]

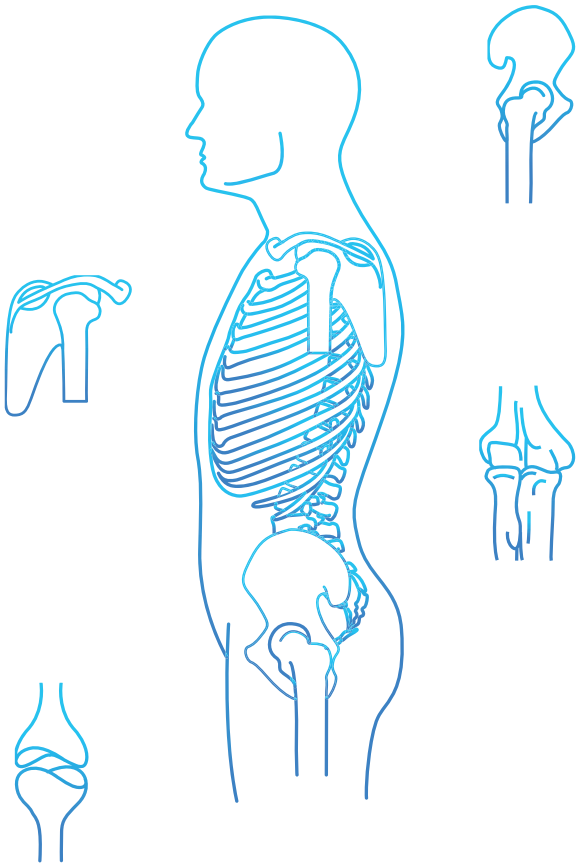
Do you smoke or have any of the following conditions?

TREATMENT FRAMEWORK

Osteoporosis

Osteoporosis is an age-related progressive bone disease characterized by the reduced bone formation and the accumulation of adipocytes in the bone marrow compartment, causing the bones to become porous and weak. Epigenetic mechanisms play a significant role in the activity of bone cells.

Diseased patients suffer from changes in the way their DNA is methylated, causing the acceleration of the disease. Those who have an accelerated epigenetic age are more likely to experience the disease. Notably, age is the most important risk factor for osteoporosis.



Adipocytes are derived from mesenchymal stem cells, which are important for making and repairing skeletal tissue. At the expense of bone formation, osteoporosis aberrant lineage allocation of mesenchymal stem cells leads to the overwhelming accumulation of marrow adipose tissue. The over-accumulation of marrow adipose tissue occurs in states of low bone density and can be harmful to the overall health of the diseased individual.

Marrow adipose tissue influences mesenchymal stem cell lineage decisions. The bone responds to various environmental cues during aging. Epigenetic regulation of mesenchymal stem cell lineage specification plays a role in osteoporosis, resulting in a mesenchymal stem cell shift from osteolineage to adipocytes. These changes can lead to a bone matrix that becomes thin and porous.[83]

Bone tissue samples from patients with osteoporosis and healthy patients uncovered inhibitors of bone formation with methylation levels being significantly different between osteoporotic and control patients. Epigenetic events may have a profound effect on the differentiation and activity of the cells within the bone marrow environment and consequently may contribute to the pathophysiology of age-related bone loss. [46]

TREATMENT FRAMEWORK

Hypertension

Hypertension is a complex condition with no single causative agent, remaining one of the world's leading health problems. It is high blood pressure characterized by the long-term force of the blood against the artery walls, causing major health problems, such as heart disease.

Evidence supports that epigenetic modifications are just as important as any genetic predisposition for the development of hypertension. The interaction between genetic and environmental systems can determine an individual's risk for hypertension.

Different degrees of DNA methylation have been correlated with the onset, timing, and severity of hypertension. Age acceleration in terms of the differences between the age predicted by DNA methylation and chronological age is an independent predictor of all-cause and cause-specific mortality in patients with hypertension.

Global genomic DNA methylation can be quantified by measuring the amount of the 5-methyl cytosines present in a DNA sample. A study found a correlation between the decreased levels of 5-methylcytosine in peripheral blood with an increase in hypertension grade severity. Global DNA methylation levels decreased as the severity of hypertension increased [81].

An effective study involving the methylation in blood pressure regulation performed a genome-wide association and were identified. Their results show the roles of DNA methylation in blood pressure regulation. Genetic variants, at 12 new loci that correlated with blood pressure modulation in 320,251 individuals of East Asian, European, and South Asian ancestry. At some of the loci, they identified DNA methylation may lie on the regulatory pathway linking sequence variation to blood pressure [42].

TREATMENT FRAMEWORK

Diabetes Mellitus

Type 2 diabetes is characterized by chronic hyperglycemia due to impaired insulin secretion. As a result of a worldwide aging population and increasing prevalence of obesity, the number of patients with type 2 diabetes has rapidly increased. Genome-wide association studies have shown that an individual's genetic background can influence the risk of this disease.

Epigenetics may affect the pathogenesis of type 2 diabetes. To determine the epigenetic basis of type-2 diabetes, a study analyzed DNA methylation at 479,927 CpG sites in human pancreatic islets, which are regions of the pancreas that produce endocrine cells, from 15 type 2 diabetic donors and 34 non-diabetic donors.

An analysis was ran to find absolute differences in DNA methylation that was greater than 5%. 1,649 CpG sites had absolute differences in methylation between the diabetic and non-diabetic islets. Of these CpG sites 97% showed a decrease in DNA methylation within the diabetic islets compared to the non-diabetic islets. The majority of the CpG sites that showed decreased DNA methylation in the diabetic islets had an intermediate degree of methylation, with 20-70% being methylated, and were more dynamic to change in human islets.

The study also found that islet expression involved in *de novo* DNA methylation correlated negatively with age. Age was associated with differential DNA methylation of 28 CpG sites and ~92% of CpG sites exhibited differential DNA methylation due to increasing age. These findings suggest that increased aging affects DNA methylation of CpG sites in the diabetic islets. [14]

It has been suggested that epigenetic changes can contribute to the occurrence of comorbid diseases. Another study found that epigenetic changes, especially after stress, can be of importance in the pathogenesis of both type 2 diabetes and depression.

Alterations in gene expression were found in postmortem specimens from a person with type 2 diabetes compared to controls without diabetes. There is a possibility for epigenetic mechanisms to explain the increased risk of dementia among individuals with diabetes. Epigenetic mechanisms explain the increased prevalence and incidence of depression among people with diabetes as well [3].

TREATMENT FRAMEWORK

Schizophrenia

The majority of deaths in schizophrenic patients have been attributed to age-related diseases that are primarily independent of the brain, such as cardiovascular and respiratory diseases. Due to accelerated biological aging in the schizophrenic population, there is an increased prevalence of these age-related disabilities and morbidities.

A study on epigenetic aging in blood affected by schizophrenia found that the change in age is significantly altered by this severe mental disorder. They used a novel blood-based DNA methylation test to be a strong predictor of morbidity and mortality. It was noted that epigenetic age is accelerated in late adulthood for schizophrenic individuals.

Based on the biological age indicated by their genome-wide DNA methylation, schizophrenic patients were on average 1.55 years older than their chronological age.

Surprisingly they found that individuals diagnosed with schizophrenia displayed epigenetic age deceleration in young to mid-adulthood. Between these age groups of young and middle-aged adults, schizophrenic patients were on average 0.7 years younger in their biological age indicated by the level of methylation within their DNA.

Age-specific effects in schizophrenia can yield new insights that may otherwise be missed. Blood-based epigenetic aging is a heritable trait and a predictor of a wide variety of phenotypes for this population of individuals vulnerable to age-related diseases and excess mortality [65]. Understanding the epigenetic mechanisms that occur between the period of middle adulthood to late adulthood is pertinent to combatting the acceleration of aging in schizophrenic people.

TREATMENT FRAMEWORK

Insomnia

Insomnia is a common sleep disorderin which it is difficult to fall asleep and stay asleep; its symptoms are connected to a multitude of age-related conditions. Accelerated biological aging may be a mechanism through which sleep influences risk for age-related disease and early mortality.

Insomnia symptoms are both associated with an increased vulnerability to declines in mental and physical health, elevated inflammation, as well as age-related morbidity and mortality including risk for coronary heart disease and cancer. ***Cross-sectional data suggests that insomnia is linked to shorter leukocyte telomere length, which is a biomarker of aging and predictor of age-related disease risk.***

Another biomarker for aging is DNA methylation. DNA methylation can examine the contribution of environmental factors accelerating the rate of aging and sleep disturbances.

Extrinsic epigenetic age acceleration is the deviation between DNA methylation and chronological age. Insomnia symptoms are significantly associated with the extrinsic measure of age acceleration.

Sleep duration and disturbances are associated with increased epigenetic age of blood tissue and higher counts of late CD8+ T cells. These findings link insomnia with accelerated epigenetic aging and are evidence of an aged immune system. The importance of aging biology for late-life chronic diseases is that there is a growing demand to address the sleep disturbance. [9]

TREATMENT FRAMEWORK

Dementia

The current public health priority, dementia, is distinguished by the structural decline in the brain. Due to the disease's wide list of symptoms, cognitive and behavioral tests don't provide a definitive diagnosis of dementia, which addresses the importance of biomarkers able to indicate the disease state.

Age-related changes in brain structure are the focus of dementia research. Increasing age is significantly associated with the increasing prevalence and incidence rates of dementia. Finding the link between age-acceleration propagated by DNA methylation and the onset of dementia is significant for targeting therapies that can prevent the disease.

Epigenetic disruptions in the brain are observed in individuals with dementia. DNA methylation markers can reflect the biological processes that occur in the early stages of dementia. DNA methylation changes have been observed in individuals with dementia. [28]

Epigenetic evidence suggests that dementia is not a suddenly occurring and sharply delineated state, but rather it is a gradual change of crucial cellular pathways going into a dysfunctional state. Locating the physical pathway for gene-environment interactions that lead to dementia is vital.

A case using two monozygotic twins found they had very different DNA methylation in brain cortical neurons. The twin with dementia had lower methylation than the healthy twin. Reduced DNA methylation is an overall trend in brain samples of dementia patients compared to people without the disease.

Evidence suggests that epigenetics can detect, prevent, and reverse such processes before clinical dementia is detected. A study found that individual epigenetic variation is not time-bound and that epigenome differences correspond to environmental influences, such as smoking. Likewise, DNA methylation changes that occur in response to stress often occur later in life. [54]

TREATMENT FRAMEWORK

Alzheimer's Disease

Aging is tied to a number of neurodegenerative diseases that cause cognitive decline. ***Alzheimer's disease is the most common form of dementia, accounting for ~70% of all dementia cases.*** After the age of 65, the risk for developing Alzheimer's disease doubles every 5 years. The pathogenesis of Alzheimer's disease involves gene-environment interactions that can be captured by the epigenome. Patterns of DNA methylation are investigated to uncover its relationship with Alzheimer's disease.

DNA methylation levels are used to measure the age of human tissues and these variant levels of methylation are linked to the pathology of Alzheimer's disease. Aging is associated with the rapidly increasing susceptibility to Alzheimer's disease. Using DNA methylation as an indicator for the rate of disease progression, we can understand that people diagnosed with Alzheimer's disease will have a higher DNA methylation age than their chronological age.

Epigenetic age acceleration, which is the change between epigenetic age and chronological age, captures the biological age of brain tissue. Alzheimer's disease patients have biologically older brains than non-diseased individuals.

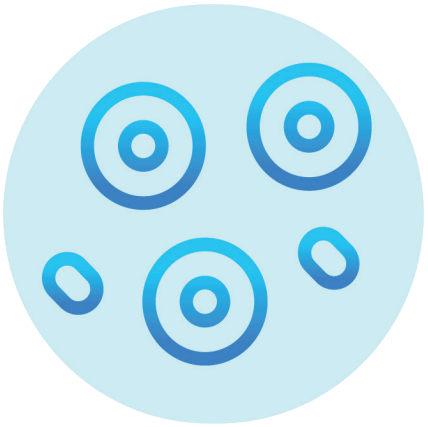
In a recent study, age indicated by methylated DNA is associated with cognitive decline among people with Alzheimer's disease. Variance in global cognitive function and episodic memory change is much higher in individuals with Alzheimer's disease than those without it. It has also been determined in this study that individuals with Alzheimer's disease experience far more cognitive aging changes than non-diseased individuals.

Alzheimer's disease is currently not treatable once patients are diagnosed, but it is definitely a preventable disease. Dietary supplements and lifestyle changes are the best measures to take when combatting Alzheimer's disease. Understanding the mechanisms that drive the acceleration of aging which contributes to the symptoms of Alzheimer's disease is pertinent when addressing the treatment and prevention of this disease. [48]

TREATMENT FRAMEWORK

Cancer Risk

As we have mentioned, the epigenetic aging rates of all tissues are different. This is true with cancer. Epigenetic age does not always parallel chronological age, particularly in tumor samples.



This is often referred to as biological age. Furthermore, since the methods for measuring epigenetic age incorporate loci in pathways related to both cancer development and aging in general (e.g., DNA damage, cellular proliferation, and oxidative stress), it is highly possible that biological age can be a predictive biomarker for cancer risk, metastasis, and mortality in addition to serving as an indicator of aging.

With further study and refinement, the concept of epigenetic age may also be useful for improving our understanding of mechanisms by which age and cancer are related. However, no longitudinal analysis has yet evaluated how blood epigenetic age changes overtime prior to cancer diagnosis or cancer-related death, and whether blood biological age can predict future risk of cancer incidence and mortality.

In one study though, they investigated patients' epigenetic markers and cancer progression were investigated. About 3–5 years before cancer onset or death, biological age was associated with cancer risks in a dose-responsive manner and a one-year increase in biological age was associated with increased cancer incidence and mortality.

Participants with smaller biological age and decelerated epigenetic aging over time had the lowest risks of cancer incidence (P = 0.003) and mortality (P = 0.02).

Although insufficientk for prediction, it was concluded that blood epigenetic age may mirror epigenetic abnormalities related to cancer development and might potentially serve as a minimally invasive biomarker for cancer early detection. [85]

TREATMENT FRAMEWORK

Breast cancer's link

As per a study conducted in 2017, increased breast cancer risk has been correlated to increased epigenetic aging rate in women who are postmenopausal (particularly intrinsic epigenetic aging rate). Yet, is another reason to attempting to reduce your aging rate. [20]

Lung cancer incidence

A separate study by Levine et al in 2015 showed a correlation between lung cancer risk and intrinsic epigenetic aging. [47]

TREATMENT FRAMEWORK

Medications

GH, DHEA, Metformin (The Famous TRIIM Study)

Are you taking growth hormone or a growth hormone secretagogue?

In mammals, the thymus supports the maturation of thymocytes into T-cells and to maintain immunological tolerance. This is an important part of what makes your immune system work.

The thymus continually atrophies after childhood. It's epithelia is replaced by adipose tissue, and it has been hypothesized that some immune dysfunction associated with aging is caused by the loss of thymus tissue. For example, infants whose thymus was removed during cardiac surgery at 18 years after surgery have immune cell populations more reminiscent of 65-70 year olds.

Multiple factors have been tested preclinically to try and regenerate the thymus. However, only one study has been shown to help regrow the thymus for immune benefit. [39]

The Impact To You

No - You mentioned that you have NOT used growth hormone or a growth hormone secretagogue. As proven in the TRIIM trial, this can be a good way to decrease the epigenetic aging rate by regenerating the thymus which atrophies as you age. This might be something to consider discussing with your physician.

TREATMENT FRAMEWORK

THE FIRST HUMAN CLINICAL TRIAL DESIGNED TO REDUCE EPIGENETIC AGE

In what may be the first human clinical trial designed to reverse aspects of human aging, the TRIIM (Thymus Regeneration, Immunorestoration, and Insulin Mitigation) study was conducted to address the thymus regeneration and help with epigenetic aging. The decision was to use GH, DHEA, and metformin.

The scientific justification for using GH to regrow thymic tissue when it has not completely atrophied is extensive, as the thymic epithelia not only express GH receptors, but also secretes GH in a positive feedback loop.

Fahy et al. treated 9 subjects in this uncontrolled Phase I trial with GH. Because GH induces hyperinsulinemia, GH was supplemented with metformin, an AMPK activator that increases glucose tolerance and DHEA, an endogenous steroid hormone that decreases gradually in adults, that can act as a precursor to testosterone, estrogen, as a neurosteroid that Fahy has stated to have anti-diabetic properties, but there is little reported evidence for this.

After treatment of 9 patients for 12 months, the thymic fat-free fraction (TFFF) (a measure of functional thymus tissue) increased significantly in 7 out of 9 participants, and in many cases almost doubling from 20% to ~35%. The two nonresponders were actually participants who had the highest TFFF at the start of the trial. These results were considered statistically significant but suffered from the underpowered number of participants.

The most significant immune changes observed were decreases in total CD38+ monocytes which were statistically correlated with the TFFF. The reduction led to an increase in the lymphocyte-to-monocyte ratio (LMR), which reached ratios similar to younger adults. ***These changes are consistent with restored thymic function.***

Because GH acts predominantly through induction of IGF-1, Fahy et al. wanted to ensure that they did not accelerate aging. Currently, various DNAm age clocks are the best correlated biomarkers available for chronological age, phenotypic age, and mortality. To their surprise, DNA age using leukocytes at 12 months of treatment was reversed in all four clocks studied with a mean change, using regression on all 4 clocks, of -2.5 years. These included the Horvath clock[9] which can predict chronological age for a large number of tissues (-2.5 years), the Hannum clock (- 3 years) which is based on leukocytes in whole blood, the phenoage DNAm clock (-3.5 years), which is better correlated with aging phenotype and the GrimAge DNAm clock (-2 years) which predicts human life expectancy. After cessation of treatment, all of the clocks resumed ticking, except the Grimage clock, which did not advance. The rates of decline increased in the last 9-12 month period which could indicate further gains are possible with longer treatment.

It is interesting that two of the three factors decrease with age (GH and DHEA) as might be expected for factors that help maintain homeostasis. It also might give some credence to hormone replacement therapies. [23]

TREATMENT FRAMEWORK

Are you taking metformin?

Metformin, an FDA approved first-line drug for the treatment of type 2 diabetes, has known beneficial effects on glucose metabolism.

Evidence from animal models and in vitro studies suggest that, in addition to its effects on glucose metabolism, metformin may influence metabolic and cellular processes associated with the development of age-related conditions such as: inflammation, oxidative damage, diminished autophagy, cell senescence, and apoptosis. Metformin is of particular interest in clinical translational research in aging since it may influence fundamental aging factors that underlie multiple age-related conditions. [4] Also, in the hallmark Fahy trial, it was part of the drug cocktail which was wildly successful in reducing the epigenetic aging rate. [23]

So does metformin have an effect on epigenetic aging? Thhe answer is probably not.

In one study, no significant differences were found for the two metformin groups, and in most cases those currently on metformin had a somewhat higher epigenetic aging rate than those who would be prescribed metformin in the future.

Also, the study's results for the extrinsic epigenetic aging rate show very little difference between those who start metformin between first and second blood draw and those who don't. [72]

The Impact To You

No - You mentioned that you have NOT used metformin. Metformin was one of the medications the TRIIM Trial used to reduce epigenetic age. This might be a medication that could help ***positively affect*** your epigenetic aging rate.

TREATMENT FRAMEWORK

Death

No one likes to talk about death, but it is an important outcome metric when considering your health and preventative health. This is also an outcome that many have focused on in the field of Epigenetic aging.

There are multiple studies that link aging rates and the risk of death. ***Soon, TruDiagnostic will have a mortality predictor to help determine your risk.*** In the meantime, we have summarized some of the findings from the literature below.

General correlations:

"Increased Age Acceleration has been associated with increased risk of mortality, and these associations, albeit small, were independent of known mortality risk factors, including a large number of demographic, lifestyle, and anthropometric variables, and medical conditions." [18]

Both intrinsic and extrinsic measures of epigenetic age acceleration in the blood are associated with an increased risk of death from all-natural causes, even after accounting for known risk factors.(111)

The different types of tests:

There are many algorithms that can help you predict death risk. The good news is that almost all measures are fairly accurate at predicting life expectancy.

A meta-analysis of blood DNA methylation data from more than 13,000 individuals found that all measures of age acceleration considered were able to predict life expectancy.

Intrinsic versus extrinsic:

Generally, intrinsic measures of epigenetic age exhibit much weaker associations with lifestyle factors and markers of inflammation, which relates to an innate aging process that doesn't capture other comorbidities. As a result, extrinsic age tends to be more predictive of death.

The measure of extrinsic age acceleration also reflects aspects of immunosenescence. This is because, by construction, it correlates with age-related changes in blood cell composition, such as T lymphocyte populations, which underlie much of the age-related decline in the protective immune response. [22]

TREATMENT FRAMEWORK

It also means that the highly predictive significance of EEA for all-cause mortality probably reflects the fact that it assesses multiple aspects of the biological age of the immune system including both changes in the blood cells.

This data also suggests that intrinsic epigenetic age acceleration is reflective of an intrinsic epigenetic clock that is associated with mortality independent of chronological age, changes in blood cell composition, and traditional risk factors of mortality.

This means that it also is probably indicative of a process of aging not related to cell composition and is still useful. For instance, IEA but not EEA is predictive of lung cancer. [47]

Additionally, IEA is also related to centenarian status. [33]

Methylation + Biomarkers = better death prediction capabilities:
Methods of biological testing, which use biological methylation markers and other covariates such as blood. Levels, fasting glucose, and albumin, tend to be even better at predicting death than just looking at methylation alone. Currently, the best biomarkers seem to be C-reactive protein, insulin, fasting glucose, triglyceride, and high-density lipoprotein (HDL) cholesterol levels.

Methylation Biomarkers + Demographics:
In 2019, a test called GrimAge was published by Dr. Steve Horvath (One of the creators of the original Biological age clocks). This is one of the best death prediction calculator to date.

Instead of using biomarkers in his calculation, he trained blood biomarkers against the epigenetic data. He created biomarkers that could be read from methylation data. This was a vast improvement and allowed for the best measurement of death prediction.

Beyond lifespan prediction, age gcceleration with GrimAge (and several of its underlying surrogate biomarkers including DNAm PAI-1) relate to many age-related conditions (multi-morbidity, metabolic syndrome, markers of inflammation) in an expected way, i.e. high values are associated with a bad risk profile.

Soon TruDiagnostic™ will have a similar test!

YOUR TREATMENT FRAMEWORK

Fitness

- You mentioned that you participate in strength exercise. It is important to get a diverse type of exercise in order to change methylation epigenetic markers in association with aging. Consider alternating the types of exercise you do.

- You mentioned that you exercise 5-7 times per week. Epigenetic study data suggests that exercising 4 times per week is the target minimum to reduce epigenetic aging.

- Epigenetic markers of exercise are more changeable and predictive of as you age. As you get older, you should make sure you work out regularly.

Medications

- You stated that you take Resveratrol. Consult with your doctor about taking a dditional supplements and medications of these types, as they have shown to slow the rate of aging.

- Ask your doctor about
growth hormone optimization to regenerate the thymus.

Psychosocial

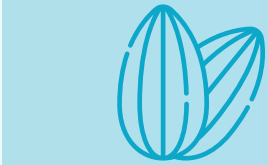
- Physical and emotional stress have been shown to increase epigenetic aging. Consider what you need to do to keep your subjective level of stress to a 2-3.

Comorbidities

- Continue to avoid behaviors that increase your risk of type 2 diabetes and obesity.

- You mentioned that you sleep 6-8 hours a night. Insomnia and low amounts of sleep have been associated with age acceleration. Consider what you need to do to get at least 7 hours of sleep each night.

- Continue to avoid behaviors that increase your risk of viruses.



Nutrition

- You mentioned that your diet mostly consists of meat and vegetables. Fish and poultry have shown to lower epigenetic age. Try incorporating more of these foods into your diet.

- Consider a calorie restriction diet, Mediterranean diet, or fasting mimicking diet with the help of a nutrional professional.

- Consider increasing your consumption of polyphenols such as trans-resveratol, sulforaphane, epigallocatechin -3-gallate (EGCG), quercetin, and genistein.

Exposures (Toxins, Pollution)

- Wear a mask in highly polluted areas

- PM2.5 particle matter data for your zip code can be found online. Create a treatment plan with your physician to avoid this type of pollution.

- Avoid exposures to pesticides and pesticide treated foods without washing them.

KEY TERMS
& Abbreviation

CMV (cytomegalovirus): a common virus that typically only causes problems for immunocompromised and pregnant individuals

CpG: regions of DNA where a cytosine (C) nucleotide is next to a guanine (C) nucleotide. It is sited in the DNA where methylation does occur.

CR (Calorie Restrictive): type of diet when you reduce the average daily caloric intake below what is normal for that particular individual

CRP (C-Reactive Protein): a protein made by the liver, measuring amounts of it in the blood is used to detect inflammation

DHA (docosahexaenoic acid): an omega-3 fatty acid that's a structural component of the brain, cerebral cortex, skin, and retina

DHEA (dehydroepiandrosterone): an endogenous steroid hormone that decreases gradually in adults, that can act as a precursor to testosterone, estrogen, as a neurosteroid

DNA Methylation: where methyl groups are added to the DNA and can change the expression of that segment without altering the sequence

EGCG (epigallocatechin-3-gallate): compound used for preventing certain diseases by targeting epigenetic alterations

EEAA (Extrinsic Epigenetic Age Acceleration): aims to measure aging in immune-related components; it also relates age-associated changes in blood cell composition.

EPA (eicosapentaenoic acid): an omega-3 fatty acid that is prescribed to reduce triglyceride levels

Epigenome: all of the chemical modifications to DNA that regulates the expression of genes

EWAS (epigenome-wide association studies): analyzes epigenetic markers, typically a DNA methylation marker, to derive epigenetic variations and a particular phenotype

FMD (fasting Mimicking diet): developed by Dr. Valter Longo, it is a 5-day diet that guides the body into a fasting state, similar to long fasts, while eating quantified meals

GH (growth hormone): a peptide hormone that stimulates growth, development, cell reproduction, and cell regeneration

HDL (high-density lipoprotein): known as the "good" cholesterol because it removes other forms of cholesterol from the body

HIV (human immunodeficiency virus): this is a family of viruses that damage to the immune system, which inhibits the body to fight off infections

Hypogonadism: the testes are no longer to produce testosterone, sperm, or both

Hypothyroidism: a condition where the thyroid gland doesn't produce enough of the body's essential hormones

IGF-1 (Insulin-like growth factor-1): a hormone that promotes bone and tissue growth

KEY TERMS
& Abbreviation

IEAA (Intrinsic Epigenetic Age Acceleration): a measure of the "pure" epigenetic aging effects in blood cells that are not confounded by differences in blood cell counts

ORA (Cooperative Health Research in the Region Augsburg): a regional-research platform for population-based studies in epidemiology and health care research

LMR (lymphocyte-to-monocyte ratio): reflects systematic inflammation in several tumors

NAS (Normative-aging Study): a longitudinal study on the effects of aging covering a variety of health issues

Metformin: a diabetes medication that regulates blood sugar levels

Nephropathy: a kidney disease caused by damage to the small blood vessels

PAI-1 (Plasminogen activator inhibitor-1): a biomarker for multiple age-related conditions

PM2.5 (PM2.5 PM2.5): refers to atmospheric particulate matter (PM) with a diameter less than 2.5 micrometers

Polyphenols: micronutrients packed with antioxidants and other health benefits

PTSD (post-traumatic stress disorder): mental health disorder that is triggered by a terrifying event that an individual either experienced or witnessed

Resveratrol: a group of polyphenols; acts like antioxidants by protecting the body against damage that puts one at risk for diseases like cancer and heart disease

SAAF (Strong African American Families Program): an intervention program meant to improve supporting parent relationships

Sarcopenia: syndrome marked by the general loss of skeletal muscle mass and strength

Segmental progeria: a rare hereditary disease that's symptoms resemble enhanced aging; most who are diagnosed don't live past their teens

Senescent cells: a state where certain cells are no longer able to divide; this arrest mechanism acts as a protectant against cancer

SES (Socioeconomic Status): social standing or class of an individual; combines education, income, and occupation

TFFF (thymic fat-free fraction): measures the functional thymus tissue

Toxoplasmosis: a disease that results from infection with the toxoplasma gondii parasite, which is one of the world's most common parasites

Triglyceride: a chemical ester of glycerol and three fatty acids

TRIMM study (Triggers and Mechanisms of Myocardial Infarction): a study of the factors associated with the transition from chronic coronary artery disease to acute myocardial infarction

UNESCO (United Nations Education, Scientific, and Cultural Organization): this is a specialized agency of the United Nations

REFERENCES

1. Agha, G., Mendelson, M. M., Ward-Caviness, C. K., Joehanes, R., Huan, T., Gondalia, R., … Baccarelli, A. A. (2019). Blood Leukocyte DNA Methylation Predicts Risk of Future Myocardial Infarction and Coronary Heart Disease. *Circulation, 140*(8), 645–657. https://doi.org/10.1161/CIRCULATIONAHA.118.039357
2. Alegría-Torres, J. A., Baccarelli, A., & Bollati, V. (2011). Epigenetics and lifestyle. *Epigenomics, 3*(3), 267–277. https://doi.org/10.2217/epi.11.22
3. Berge, L. I., & Riise, T. (2015). Comorbidity between type 2 diabetes and depression in the adult population: directions of the association and its possible pathophysiological mechanisms. *International journal of endocrinology, 2015.* https://doi.org/10.1155/2015/164760
4. Barzilai, N., Crandall, J. P., Kritchevsky, S. B., & Espeland, M. A. (2016). Metformin as a Tool to Target Aging. Cell Metabolism, 23(6), 1060–1065. https://doi.org/https://doi.org/10.1016/j.cmet.2016.05.011
5. Bohacek, J., & Mansuy, I. M. (2013). Epigenetic inheritance of disease and disease risk. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 38(1), 220–236. https://doi.org/10.1038/npp.2012.110
6. Breuss, J. M., Atanasov, A. G., & Uhrin, P. (2019). Resveratrol and Its Effects on the Vascular System. International journal of molecular sciences, 20(7), 1523. https://doi.org/10.3390/ijms20071523
7. Brody, G. H., Miller, G. E., Yu, T., Beach, S. R., & Chen, E. (2016). Supportive Family Environments Ameliorate the Link Between Racial Discrimination and Epigenetic Aging: A Replication Across Two Longitudinal Cohorts. Psychological science, 27(4), 530–541. https://doi.org/10.1177/0956797615626703
8. Bush, N. R., Edgar, R. D., Park, M., MacIsaac, J. L., McEwen, L. M., Adler, N. E., Essex, M. J., Kobor, M. S., & Boyce, W. T. (2018). The biological embedding of early-life socioeconomic status and family adversity in children's genome-wide DNA methylation. Epigenomics, 10(11), 1445–1461. https://doi.org/10.2217/epi-2018-0042
9. Carroll, J. E., Irwin, M. R., Levine, M., Seeman, T. E., Absher, D., Assimes, T., & Horvath, S. (2017). Epigenetic Aging and Immune Senescence in Women With Insomnia Symptoms: Findings From the Women's Health Initiative Study. Biological Psychiatry, 81(2), 136–144. https://doi.org/https://doi.org/10.1016/j.biopsych.2016.07.008
10. Chen, Edith et al. "The Great Recession and health risks in African American youth." Brain, behavior, and immunity vol. 53 (2016): 234-241. https://doi.org/10.1016/j.bbi.2015.12.015
11. Chen, B. H., Marioni, R. E., Colicino, E., Peters, M. J., Ward-Caviness, C. K., Tsai, P. C., Roetker, N. S., Just, A. C., Demerath, E. W., Guan, W., Bressler, J., Fornage, M., Studenski, S., Vandiver, A. R., Moore, A. Z., Tanaka, T., Kiel, D. P., Liang, L., Vokonas, P., Schwartz, J., … Horvath, S. (2016). DNA methylation-based measures of biological age: meta-analysis predicting time to death. Aging, 8(9), 1844–1865. https://doi.org/10.18632/aging.101020
12. Christiansen, L., Lenart, A., Tan, Q., Vaupel, J. W., Aviv, A., McGue, M., & Christensen, K. (2016). DNA methylation age is associated with mortality in a longitudinal Danish twin study. Aging cell, 15(1), 149–154. https://doi.org/10.1111/acel.12421
13. Crews D. (2010). Epigenetics, brain, behavior, and the environment. Hormones (Athens, Greece), 9(1), 41–50. https://doi.org/10.14310/horm.2002.1251

REFERENCES

14. Dayeh, T., Volkov, P., Salö, S., Hall, E., Nilsson, E., Olsson, A. H., … Ling, C. (2014). Genome-Wide DNA Methylation Analysis of Human Pancreatic Islets from Type 2 Diabetic and Non-Diabetic Donors Identifies Candidate Genes That Influence Insulin Secretion. PLOS Genetics, 10(3), e1004160. Retrieved from https://doi.org/10.1371/journal.pgen.1004160
15. Dhingra, R., Nwanaji-Enwerem, J. C., Samet, M., & Ward-Caviness, C. K. (2018). DNA Methylation Age-Environmental Influences, Health Impacts, and Its Role in Environmental Epidemiology. Current environmental health reports, 5(3), 317–327. https://doi.org/10.1007/s40572-018-0203-2
16. Du, Y., Xu, X., Chu, M., Guo, Y., & Wang, J. (2016). Air particulate matter and cardiovascular disease: the epidemiological, biomedical and clinical evidence. Journal of thoracic disease, 8(1), E8–E19. https://doi.org/10.3978/j.issn.2072-1439.2015.11.37
17. Dugué, P.-A., Bassett, J. K., Joo, J. E., Baglietto, L., Jung, C.-H., Wong, E. M., … Milne, R. L. (2017). Association of DNA Methylation-Based Biological Age With Health Risk Factors and Overall and Cause-Specific Mortality. American Journal of Epidemiology, 187(3), 529–538. https://doi.org/10.1093/aje/kwx291
18. Dunn, E. C., Soare, T. W., Zhu, Y., Simpkin, A. J., Suderman, M. J., Klengel, T., … Relton, C. L. (2019). Sensitive Periods for the Effect of Childhood Adversity on DNA Methylation: Results From a Prospective, Longitudinal Study. Biological Psychiatry, 85(10), 838–849. https://doi.org/10.1016/j.biopsych.2018.12.023
19. Durso, D. F., Bacalini, M. G., Sala, C., Pirazzini, C., Marasco, E., Bonafé, M., do Valle, Í. F., Gentilini, D., Castellani, G., Faria, A., Franceschi, C., Garagnani, P., & Nardini, C. (2017). Acceleration of leukocytes' epigenetic age as an early tumor and sex-specific marker of breast and colorectal cancer. Oncotarget, 8(14), 23237–23245. https://doi.org/10.18632/oncotarget.15573
20. Essex, M. J., Boyce, W. T., Hertzman, C., Lam, L. L., Armstrong, J. M., Neumann, S. M., & Kobor, M. S. (2013). Epigenetic vestiges of early developmental adversity: childhood stress exposure and DNA methylation in adolescence. Child development, 84(1), 58–75. https://doi.org/10.1111/j.1467-8624.2011.01641.x
21. Fagnoni, F. F., Vescovini, R., Passeri, G., Bologna, G., Pedrazzoni, M., Lavagetto, G., Casti, A., Franceschi, C., Passeri, M., & Sansoni, P. (2000). Shortage of circulating naive CD8(+) T cells provides new insights on immunodeficiency in aging. Blood, 95(9), 2860–2868.
22. Fahy, G. M., Brooke, R. T., Watson, J. P., Good, Z., Vasanawala, S. S., Maecker, H., … Horvath, S. (2019). Reversal of epigenetic aging and immunosenescent trends in humans. Aging Cell, 18(6), e13028. https://doi.org/10.1111/acel.13028
23. Flatt T. (2012). A new definition of aging?. Frontiers in genetics, 3, 148. https://doi.org/10.3389/fgene.2012.00148
24. Fiorito, G., Polidoro, S., Dugué, P. A., Kivimaki, M., Ponzi, E., Matullo, G., Guarrera, S., Assumma, M. B., Georgiadis, P., Kyrtopoulos, S. A., Krogh, V., Palli, D., Panico, S., Sacerdote, C., Tumino, R., Chadeau-Hyam, M., Stringhini, S., Severi, G., Hodge, A. M., Giles, G. G., … Vineis, P. (2017). Social adversity and epigenetic aging: a multi-cohort study on socioeconomic differences in peripheral blood DNA methylation. Scientific reports, 7(1), 16266. https://doi.org/10.1038/s41598-017-16391-5

REFERENCES

25. Franceschi, C., Bonafè, M., Valensin, S., Olivieri, F., De Luca, M., Ottaviani, E., & De Benedictis, G. (2000). Inflamm-aging. An evolutionary perspective on immunosenescence. Annals of the New York Academy of Sciences, 908, 244–254. https://doi.org/10.1111/j.1749-6632.2000.tb06651.x

26. Franceschi C. (2007). Inflammaging as a major characteristic of old people: can it be prevented or cured?. Nutrition reviews, 65(12 Pt 2), S173–S176. https://doi.org/10.1111/j.1753-4887.2007.tb00358.x

27. Fransquet, P. D., & Ryan, J. (2019). The current status of blood epigenetic biomarkers for dementia. Critical Reviews in Clinical Laboratory Sciences, 56(7), 435–457. https://doi.org/10.1080/10408363.2019.1639129

28. Gao, X., Zhang, Y., Breitling, L. P., & Brenner, H. (2016). Relationship of tobacco smoking and smoking-related DNA methylation with epigenetic age acceleration. Oncotarget, 7(30), 46878–46889. https://doi.org/10.18632/oncotarget.9795

29. Gensous, N., Garagnani, P., Santoro, A., Giuliani, C., Ostan, R., Fabbri, C., … Bacalini, M. G. (2020). One-year Mediterranean diet promotes epigenetic rejuvenation with country- and sex-specific effects: a pilot study from the NU-AGE project. GeroScience, 42(2), 687–701. https://doi.org/10.1007/s11357-019-00149-0

30. Hahn, O., Grönke, S., Stubbs, T. M., Ficz, G., Hendrich, O., Krueger, F., Andrews, S., Zhang, Q., Wakelam, M. J., Beyer, A., Reik, W., & Partridge, L. (2017). Dietary restriction protects from age-associated DNA methylation and induces epigenetic reprogramming of lipid metabolism. Genome biology, 18(1), 56. https://doi.org/10.1186/s13059-017-1187-1

31. Horvath, S., & Levine, A. J. (2015). HIV-1 Infection Accelerates Age According to the Epigenetic Clock. The Journal of infectious diseases, 212(10), 1563–1573. https://doi.org/10.1093/infdis/jiv277

32. Horvath, S., Pirazzini, C., Bacalini, M. G., Gentilini, D., Di Blasio, A. M., Delledonne, M., Mari, D., Arosio, B., Monti, D., Passarino, G., De Rango, F., D'Aquila, P., Giuliani, C., Marasco, E., Collino, S., Descombes, P., Garagnani, P., & Franceschi, C. (2015). Decreased epigenetic age of PBMCs from Italian semi-supercentenarians and their offspring. Aging, 7(12), 1159–1170. https://doi.org/10.18632/aging.100861

33. Horvath, S., Garagnani, P., Bacalini, M. G., Pirazzini, C., Salvioli, S., Gentilini, D., … Franceschi, C. (2015). Accelerated epigenetic aging in Down syndrome. Aging Cell, 14(3), 491–495. https://doi.org/10.1111/acel.12325

34. Horvath, S., Gurven, M., Levine, M. E., Trumble, B. C., Kaplan, H., Allayee, H., Ritz, B. R., Chen, B., Lu, A. T., Rickabaugh, T. M., Jamieson, B. D., Sun, D., Li, S., Chen, W., Quintana-Murci, L., Fagny, M., Kobor, M. S., Tsao, P. S., Reiner, A. P., Edlefsen, K. L., … Assimes, T. L. (2016). An epigenetic clock analysis of race/ethnicity, sex, and coronary heart disease. Genome biology, 17(1), 171. https://doi.org/10.1186/s13059-016-1030-0

35. Howitz, K. T., Bitterman, K. J., Cohen, H. Y., Lamming, D. W., Lavu, S., Wood, J. G., … Sinclair, D. A. (2003). Small molecule activators of sirtuins extend Saccharomyces cerevisiae lifespan. Nature, 425(6954), 191–196. https://doi.org/10.1038/nature01960

36. Isaksen, J., Bryn, V., Diseth, T. H., Heiberg, A., Schjølberg, S., & Skjeldal, O. H. (2013). Children with autism spectrum disorders – The importance of medical investigations. European Journal of Paediatric Neurology, 17(1), 68–76. https://doi.org/https://doi.org/10.1016/j.ejpn.2012.08.004

37. Javed, R., Chen, W., Lin, F., & Liang, H. (2016). Infant's DNA Methylation Age at Birth and Epigenetic Aging Accelerators. BioMed research international, 2016, 4515928. https://doi.org/10.1155/2016/4515928

REFERENCES

38. Jawa, V., Cousens, L. P., Awwad, M., Wakshull, E., Kropshofer, H., & De Groot, A. S. (2013). T-cell dependent immunogenicity of protein therapeutics: Preclinical assessment and mitigation. Clinical Immunology, 149(3, Part B), 534–555. https://doi.org/https://doi.org/10.1016/j.clim.2013.09.006

39. Jylhävä, J., Hjelmborg, J., Soerensen, M., Munoz, E., Tan, Q., Kuja-Halkola, R., … Reynolds, C. A. (2019). Longitudinal changes in the genetic and environmental influences on the epigenetic clocks across old age: Evidence from two twin cohorts. EBioMedicine, 40, 710–716. https://doi.org/https://doi.org/10.1016/j.ebiom.2019.01.040

40. Kananen, L., Nevalainen, T., Jylhävä, J., Marttila, S., Hervonen, A., Jylhä, M., & Hurme, M. (2015). Cytomegalovirus infection accelerates epigenetic aging. Experimental gerontology, 72, 227–229. https://doi.org/10.1016/j.exger.2015.10.008

41. Kato, N., Loh, M., Takeuchi, F., Verweij, N., Wang, X., Zhang, W., Kelly, T. N., Saleheen, D., Lehne, B., Leach, I. M., Drong, A. W., Abbott, J., Wahl, S., Tan, S. T., Scott, W. R., Campanella, G., Chadeau-Hyam, M., Afzal, U., Ahluwalia, T. S., Bonder, M. J., … Chambers, J. C. (2015). Trans-ancestry genome-wide association study identifies 12 genetic loci influencing blood pressure and implicates a role for DNA methylation. Nature genetics, 47(11), 1282–1293. https://doi.org/10.1038/ng.34055

42. Kennedy, B. K., Berger, S. L., Brunet, A., Campisi, J., Cuervo, A. M., Epel, E. S., Franceschi, C., Lithgow, G. J., Morimoto, R. I., Pessin, J. E., Rando, T. A., Richardson, A., Schadt, E. E., Wyss-Coray, T., & Sierra, F. (2014). Geroscience: linking aging to chronic disease. Cell, 159(4), 709–713. https://doi.org/10.1016/j.cell.2014.10.039

43. Kulminski, A. M., Culminskaya, I. V., Ukraintseva, S. V., Arbeev, K. G., Land, K. C., & Yashin, A. I. (2008). Sex-specific health deterioration and mortality: the morbidity-mortality paradox over age and time. Experimental gerontology, 43(12), 1052–1057. https://doi.org/10.1016/j.exger.2008.09.007

44. Lawn, R. B., Anderson, E. L., Suderman, M., Simpkin, A. J., Gaunt, T. R., Teschendorff, A. E., … Howe, L. D. (2018). Psychosocial adversity and socioeconomic position during childhood and epigenetic age: analysis of two prospective cohort studies. Human Molecular Genetics, 27(7), 1301–1308. https://doi.org/10.1093/hmg/ddy036

45. Letarouilly, J. G., Broux, O., & Clabaut, A. (2019). New insights into the epigenetics of osteoporosis. Genomics, 111(4), 793–798. https://doi.org/10.1016/j.ygeno.2018.05.001

46. Levine, M. E., Hosgood, H. D., Chen, B., Absher, D., Assimes, T., & Horvath, S. (2015). DNA methylation age of blood predicts future onset of lung cancer in the women's health initiative. Aging, 7(9), 690–700. https://doi.org/10.18632/aging.100809

47. Levine, M. E., Lu, A. T., Bennett, D. A., & Horvath, S. (2015). Epigenetic age of the pre-frontal cortex is associated with neuritic plaques, amyloid load, and Alzheimer's disease related cognitive functioning. Aging, 7(12), 1198–1211. https://doi.org/10.18632/aging.100864

48. Lind, P. M., Salihovic, S., & Lind, L. (2018). High plasma organochlorine pesticide levels are related to increased biological age as calculated by DNA methylation analysis. Environment International, 113, 109–113. https://doi.org/https://doi.org/10.1016/j.envint.2018.01.019

REFERENCES

49. Longo, V. D., & Mattson, M. P. (2014). Fasting: Molecular Mechanisms and Clinical Applications. Cell Metabolism, 19(2), 181–192. https://doi.org/https://doi.org/10.1016/j.cmet.2013.12.008

50. Lu, A. T., Quach, A., Wilson, J. G., Reiner, A. P., Aviv, A., Raj, K., Hou, L., Baccarelli, A. A., Li, Y., Stewart, J. D., Whitsel, E. A., Assimes, T. L., Ferrucci, L., & Horvath, S. (2019). DNA methylation GrimAge strongly predicts lifespan and healthspan. Aging, 11(2), 303–327. https://doi.org/10.18632/aging.101684

51. Ludwig-Walz, H., Schmidt, M., Günther, A. L. B., & Kroke, A. (2018). Maternal prepregnancy BMI or weight and offspring's blood pressure: Systematic review. Maternal & Child Nutrition, 14(2), e12561. https://doi.org/10.1111/mcn.12561

52. Maierhofer, A., Flunkert, J., Oshima, J., Martin, G. M., Haaf, T., & Horvath, S. (2017). Accelerated epigenetic aging in Werner syndrome. Aging, 9(4), 1143–1152. https://doi.org/10.18632/aging.101217

53. Maloney, B., & Lahiri, D. K. (2016). Epigenetics of dementia: understanding the disease as a transformation rather than a state. The Lancet Neurology, 15(7), 760-774. https://doi.org/10.1016/S1474-4422(16)00065-X

54. Marioni, R. E., Shah, S., McRae, A. F., Chen, B. H., Colicino, E., Harris, S. E., … Deary, I. J. (2015). DNA methylation age of blood predicts all-cause mortality in later life. Genome Biology, 16(1), 25. https://doi.org/10.1186/s13059-015-0584-6

56. Martin, E. M., & Fry, R. C. (2018). Environmental Influences on the Epigenome: Exposure- Associated DNA Methylation in Human Populations. Annual Review of Public Health, 39(1), 309–333. https://doi.org/10.1146/annurev-publhealth-040617-014629

57. McGowan, P. O., Sasaki, A., D'Alessio, A. C., Dymov, S., Labonté, B., Szyf, M., Turecki, G., & Meaney, M. J. (2009). Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. Nature neuroscience, 12(3), 342–348. https://doi.org/10.1038/nn.2270

58. Medical comorbidities in autism spectrum disorders: a primer for health care professionals and policy makers. (2013). [second edition]. Retrieved from https://www.safeminds.org/wp-content/uploads/2014/10/Medical-Comorbitidies-in-ASD-2014.pdf

59. Miller, R. A. (1996). The Aging Immune System: Primer and Prospectus. Science, 273(5271), 70 LP-74. https://doi.org/10.1126/science.273.5271.70

60. Moore, S. R., McEwen, L. M., Quirt, J., Morin, A., Mah, S. M., Barr, R. G., … Kobor, M. S. (2017). Epigenetic correlates of neonatal contact in humans. Development and Psychopathology, 29(5), 1517–1538. https://doi.org/10.1017/S0954579417001213

61. Moore, A. M., Xu, Z., Kolli, R. T., White, A. J., Sandler, D. P., & Taylor, J. A. (2019). Persistent epigenetic changes in adult daughters of older mothers. Epigenetics, 14(5), 467–476. https://doi.org/10.1080/15592294.2019.1595299

62. Most, J., Tosti, V., Redman, L. M., & Fontana, L. (2017). Calorie restriction in humans: An update. Ageing research reviews, 39, 36–45. https://doi.org/10.1016/j.arr.2016.08.005

63. Nwanaji-Enwerem, J. C., Dai, L., Colicino, E., Oulhote, Y., Di, Q., Kloog, I., Just, A. C., Hou, L., Vokonas, P., Baccarelli, A. A., Weisskopf, M. G., & Schwartz, J. D. (2017). Associations between long-term exposure to PM2.5 component species and blood DNA methylation age in the elderly: The VA normative aging study. Environment international, 102, 57–65. https://doi.org/10.1016/j.envint.2016.12.024

REFERENCES

64. Okazaki, S., Otsuka, I., Numata, S., Horai, T., Mouri, K., Boku, S., … Hishimoto, A. (2019). Epigenetic clock analysis of blood samples from Japanese schizophrenia patients. Npj Schizophrenia, 5(1), 4. https://doi.org/10.1038/s41537-019-0072-1

65. Ori, A., Horvath, S., Kahn, R., & Ophoff, R. (2018). F124Epigenetic Aging in Blood is Affected in Schizophrenia. European Neuropsychopharmacology, 29, Retrieved from https://doi.org/10.1016/j.euroneuro.2018.08.204

66. Palma-Gudiel, H., Eixarch, E., Crispi, F., Morán, S., Zannas, A. S., & Fañanás, L. (2019). Prenatal adverse environment is associated with epigenetic age deceleration at birth and hypomethylation at the hypoxia-responsive EP300 gene. Clinical epigenetics, 11(1), 73. https://doi.org/10.1186/s13148-019-0674-5

67. Pandey, K. B., & Rizvi, S. I. (2009). Plant polyphenols as dietary antioxidants in human health and disease. Oxidative medicine and cellular longevity, 2(5), 270–278. https://doi.org/10.4161/oxim.2.5.9498

68. Parikshak, N. N., Swarup, V., Belgard, T. G., Irimia, M., Ramaswami, G., Gandal, M. J., … Geschwind, D. H. (2016). Genome-wide changes in lncRNA, splicing, and regional gene expression patterns in autism. Nature, 540(7633), 423–427. https://doi.org/10.1038/nature20612

69. Park, J. H., Yoo, Y., & Park, Y. J. (2017). Epigenetics: Linking Nutrition to Molecular Mechanisms in Aging. Preventive nutrition and food science, 22(2), 81–89. https://doi.org/10.3746/pnf.2017.22.2.81

70. Peng, C., Cardenas, A., Rifas-Shiman, S. L., Hivert, M. F., Gold, D. R., Platts-Mills, T. A., Lin, X., Oken, E., Avila, L., Celedón, J. C., Weiss, S. T., Baccarelli, A. A., Litonjua, A. A., & DeMeo, D. L. (2019). Epigenetic age acceleration is associated with allergy and asthma in children in Project Viva. The Journal of allergy and clinical immunology, 143(6), 2263–2270.e14. https://doi.org/10.1016/j.jaci.2019.01.034

71. Perna, L., Zhang, Y., Mons, U., Holleczek, B., Saum, K.-U., & Brenner, H. (2016). Epigenetic age acceleration predicts cancer, cardiovascular, and all-cause mortality in a German case cohort. Clinical Epigenetics, 8(1), 64. https://doi.org/10.1186/s13148-016-0228-z

72. Quach, A., Levine, M. E., Tanaka, T., Lu, A. T., Chen, B. H., Ferrucci, L., Ritz, B., Bandinelli, S., Neuhouser, M. L., Beasley, J. M., Snetselaar, L., Wallace, R. B., Tsao, P. S., Absher, D., Assimes, T. L., Stewart, J. D., Li, Y., Hou, L., Baccarelli, A. A., Whitsel, E. A., … Horvath, S. (2017). Epigenetic clock analysis of diet, exercise, education, and lifestyle factors. Aging, 9(2), 419–446. https://doi.org/10.18632/aging.101168

73. Robinson, G. E., & Barron, A. B. (2017). Epigenetics and the evolution of instincts. Science, 356(6333), 26 LP-27. https://doi.org/10.1126/science.aam6142

74. Simons, D. J., Boot, W. R., Charness, N., Gathercole, S. E., Chabris, C. F., Hambrick, D. Z., & Stine-Morrow, E. A. (2016). Do "Brain-Training" Programs Work?. Psychological science in the public interest : a journal of the American Psychological Society, 17(3), 103–186. https://doi.org/10.1177/1529100616661983

75. Smith, J. A., Raisky, J., Ratliff, S. M., Liu, J., Kardia, S. L. R., Turner, S. T., … Zhao, W. (2019). Intrinsic and extrinsic epigenetic age acceleration are associated with hypertensive target organ damage in older African Americans. BMC Medical Genomics, 12(1), 141. https://doi.org/10.1186/s12920-019-0585-5

76. Steinberg, J., Shah, K. M., Gartland, A., Zeggini, E., & Wilkinson, J. M. (2017). Effects of chronic cobalt and chromium exposure after metal-on-metal hip resurfacing: An epigenome-wide association pilot study. Journal of orthopaedic research : official publication of the Orthopaedic Research Society, 35(10), 2323–2328. https://doi.org/10.1002/jor.23525

REFERENCES

77. Steinkraus, K. A., Kaeberlein, M., & Kennedy, B. K. (2008). Replicative aging in yeast: the means to the end. Annual review of cell and developmental biology, 24, 29–54. https://doi.org/10.1146/annurev.cellbio.23.090506.123509

78. Tan, Q., Christiansen, L., Hjelmborg, J. V. B., & Christensen, K. (2015). Twin methodology in epigenetic studies. Journal of Experimental Biology, 218(1), 134–139. https://doi.org/10.1242/jeb.107151

79. Tyebji, S., Hannan, A. J., & Tonkin, C. J. (2020). Pathogenic Infection in Male Mice Changes Sperm Small RNA Profiles and Transgenerationally Alters Offspring Behavior. Cell Reports, 31(4), 107573. https://doi.org/https://doi.org/10.1016/j.celrep.2020.107573

80. Valenzuela, M. A., Canales, J., Corvalán, A. H., & Quest, A. F. (2015). Helicobacter pylori-induced inflammation and epigenetic changes during gastric carcinogenesis. World journal of gastroenterology, 21(45), 12742–12756. https://doi.org/10.3748/wjg.v21.i45.12742

81. Wise, I., & Charchar, F. (2016). Epigenetic Modifications in Essential Hypertension. International Journal of Molecular Sciences, 17(4), 451. MDPI AG. http://dx.doi.org/10.3390/ijms17040451

82. Xie, K., Ryan, D. P., Pearson, B. L., Henzel, K. S., Neff, F., Vidal, R. O., … Ehninger, D. (2018). Epigenetic alterations in longevity regulators, reduced life span, and exacerbated aging-related pathology in old father offspring mice. Proceedings of the National Academy of Sciences, 115(10), E2348 LP-E2357. https://doi.org/10.1073/pnas.1707337115

83. Yu, B., & Wang, C. Y. (2016). Osteoporosis: The Result of an 'Aged' Bone Microenvironment. Trends in molecular medicine, 22(8), 641–644. https://doi.org/10.1016/j.molmed.2016.06.002

84. Zannas, A. S., Arloth, J., Carrillo-Roa, T., Iurato, S., Röh, S., Ressler, K. J., … Mehta, D. (2015). Lifetime stress accelerates epigenetic aging in an urban, African American cohort: relevance of glucocorticoid signaling. Genome Biology, 16(1), 266. https://doi.org/10.1186/s13059-015-0828-5

85. Zheng, Y., Joyce, B. T., Colicino, E., Liu, L., Zhang, W., Dai, Q., Shrubsole, M. J., Kibbe, W. A., Gao, T., Zhang, Z., Jafari, N., Vokonas, P., Schwartz, J., Baccarelli, A. A., & Hou, L. (2016). Blood Epigenetic Age may Predict Cancer Incidence and Mortality. EBioMedicine, 5, 68–73. https://doi.org/10.1016/j.ebiom.2016.02.008

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