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PATIENT: XXXXXXXXXXXXXX			TEST REF: GNL-NL-XXXXX
TEST NUMBER: G-NL-XXXXXXX	COLLECTED: 23-Mar-2023		PRACTITIONER: SSSSSSSSSSS
GENDER: XX	RECEIVED: 01-Mar-2023		
AGE: XX	TESTED: 01-Mar-2023		XXXXXXXXXXXXXXXXXX

TEST NAME: OMICm Age Report

TRUAGE BY TRUDIAGNOSTIC

OMICm Age

This report calculates biological age by examining age-associated methylation patterns at approximately one million locations on your DNA, using the novel OMICm Age algorithm.

Developed By TruDiagnostic's Bioinformatics & Research Department

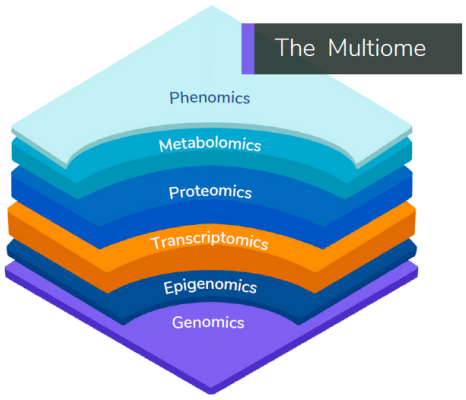
A NEW AGING ALGORITHM

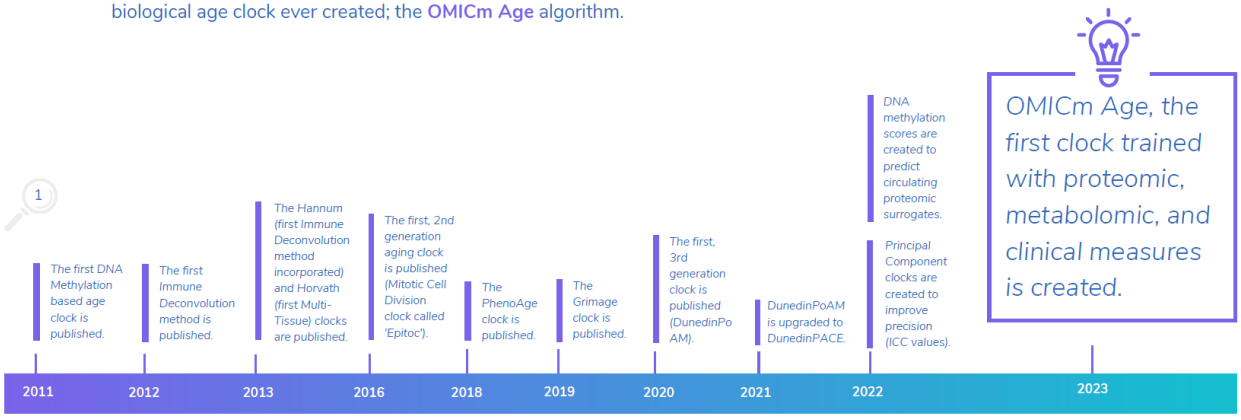
Raising the bar on measuring aging.

When TruDiagnostic was founded in 2020, we set out on a mission to create the best scientific algorithm (clock) that analyzes epigenetic patterns to accurately quantify biological age. To do this, we needed an extensive amount of data, which is why we partnered with researchers from Harvard University and Partners Biobank.

This biobank included thousands of samples saved from over the last 50 years. With these samples, **we were able to collect the extensive amount of interconnected biodata needed to create the most accurate predictors of biological aging**.

This process has taken us almost three years to finalize, but we are proud to announce the completion of the best biological age clock ever created; the **OMICm Age** algorithm.





OMICm Age, the first clock trained with proteomic, metabolomic, and clinical measures is created.

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TEST NAME: OMICm Age Report

OUR APPROACH

Multi Omics & Biological Aging.

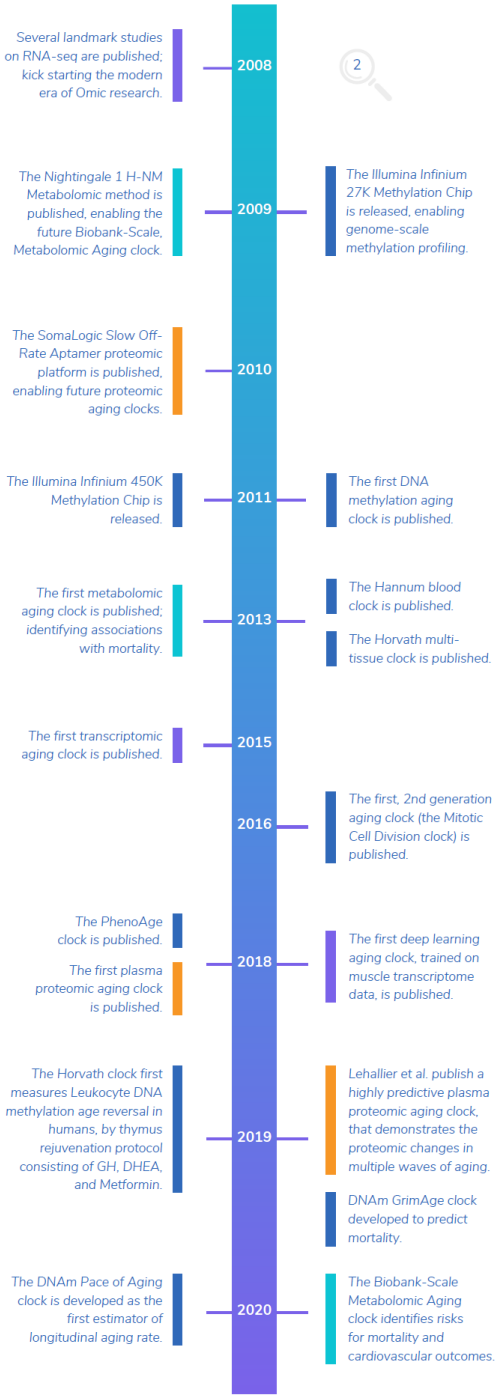
When the Human Genome Project (an initiative to map the entire human genome) was first announced decades ago, many people thought the results would inform us about everything related to human biology. While it was a great project, the actionable health information gained from its efforts left many people disappointed. One reason why is that genetic composition is only one small piece of the puzzle.

We now know that **the functionality of your body, as well as your health outcomes (phenotypes), are a result of much more than just your DNA**. Your epigenetics and transcriptome, the peptides and proteins in your body (proteome), and the metabolites from your body's processes and environmental exposures are all crucial factors in how your biology operates. This large picture of interconnected cellular processes is often called the multiome (Multi Omics) and it is a combination of all the different measurements we can perform on the body.

Thus, to create the best biological age clock, we didn't want to just measure epigenetics. We wanted to measure the entire multiome. So, we did! **In 5,000 people, we used advanced analysis techniques to quantify all biomarkers that make up the multiome." Proteins, metabolites, and DNA methylation altogether were measured in only 1500 subjects. We used these individuals to train the epigenetic biomarker proxies (EBPs) for proteins and metabolites and, later on, we quantified these EBP in the ~ 5000 subjects with DNA methylation**. We used Whole Exome Sequencing, Untargeted Plasma Proteomics, Plasma Metabolomics, as well as Clinical Data and Outcome Data for our large group (cohort). Together, this novel data allows for an unmatched resolution in quantifying the whole body's aging process. It also allows us to view aging throughout the multiome, through the lens of DNA methylation.

In our initial publication regarding the research and findings used to develop our OMICm Age algorithm, we **showed that this clock is better at predicting health and aging outcomes** than any other methylation age clock to date.

Epigenomics
Transcriptomics
Proteomics
Metabolomics



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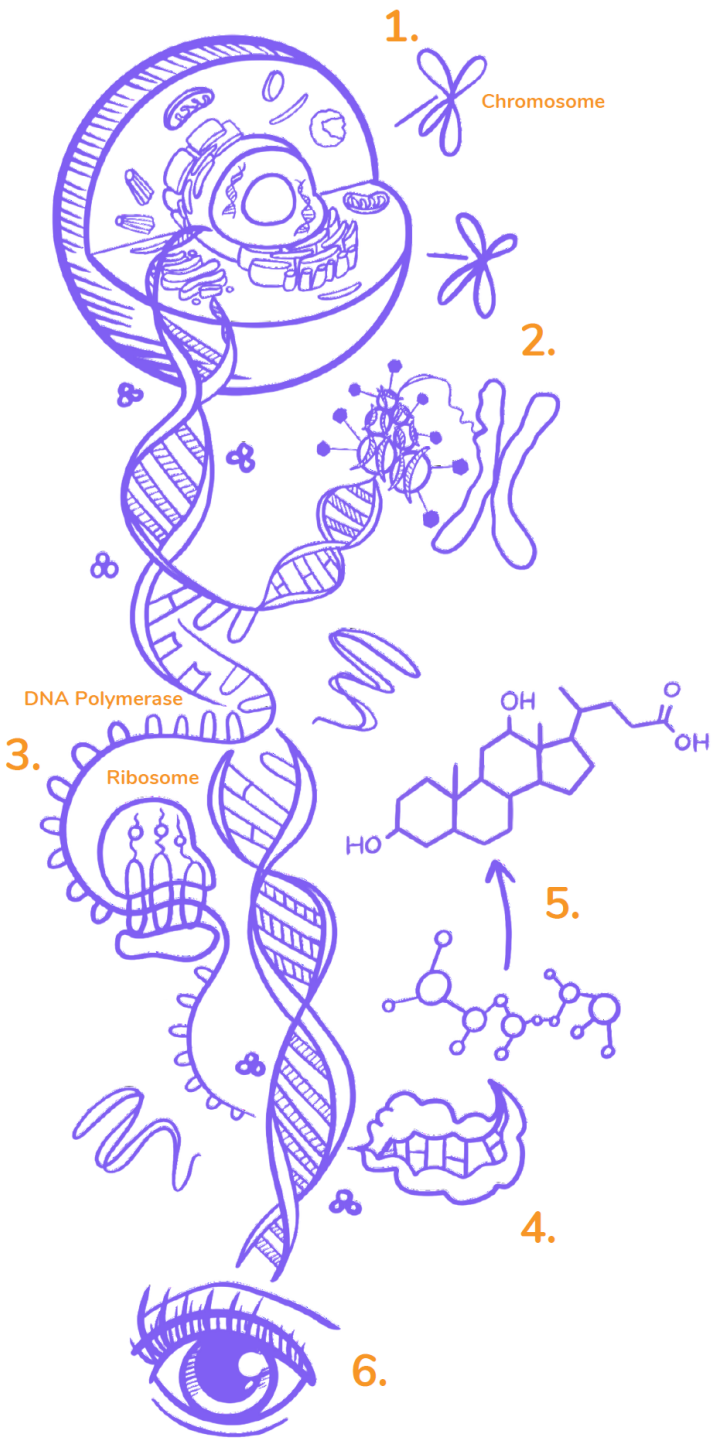

1. Genomics

The study of the genes housed in our DNA.
Our DNA, located in the nucleus of our cells, contains sections of instructions (genes) that tell a cell how to behave. Your genetics stay the same from conception to death.

2. Epigenomics

The study of how our genes are modified.
Epigenetic molecules interact with our DNA, either amplifying or silencing certain instructions. These interactions change throughout your lifetime.

3. Transcriptomics

The study of how our genes turn into actionable RNA.
During transcription, molecules called RNA copy the instructions of our DNA; skipping over or boosting sections based on the epigenetic patterns at that location.

4. Proteomics

The study of how proteins function. Proteins are created by RNA, and perform most of the work within a cell. Antibodies, enzymes, and hormones are all types of protein functions.

5. Metabolomics

The study of the chemical processes produced by protein interactions. Metabolites are a by-product of proteins hard at work, and are used to help break down food, drugs, chemicals, or the body's own tissue.

6. Phenomics

The study of observable traits such as eye, skin, and hair color. Epigenetics can curate those instructions, and the resulting proteins and metabolites impact your biology to result in a physical expression.

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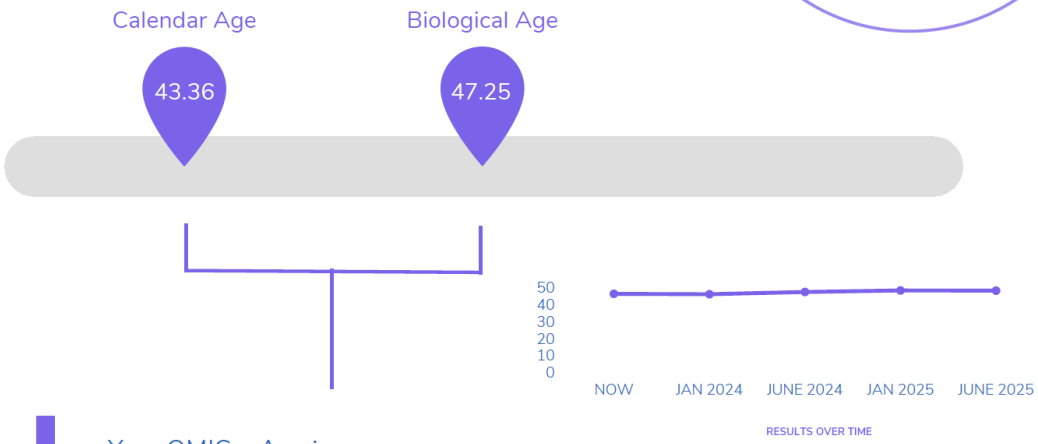
TEST NAME: OMICm Age Report

PROVIDED BY: TruDiagnostic™ The Epigenetic Company

Your Results.

DISCLAIMER: All population graphs included in this report are based off of data from thousands of research participants and TruAge test takers. Unless otherwise specified, population graphs are included to provide context to your results, but are not necessarily reflections of individual scores.

47.25
YEARS OLD
OMICm Age



RESULTS OVER TIME

Your OMICm Age is

HIGHER THAN

your calendar age by 3.89 years.

YOUR OMICm Age IS IN THE:

82nd

PERCENTILE MEANING THAT YOUR OMICm AGE IS HIGHER THAN 82% OF THE POPULATION AT YOUR SAME CHRONOLOGICAL AGE.

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TEST NAME: OMICm Age Report

YOUR RISK OF DISEASE

DISCLAIMER: The following, personalized risk scores were calculated based off of observed and validated patterns in data, from thousands of research participants involved in our Harvard University and TruDiagnostic partnered study. This cohort is believed to be a strong sample representation of larger population data.

Aging has been scientifically proven to be the number one risk factor for major chronic diseases world-wide. Accelerated aging (having an older biological age than your calendar age) increases your risk of disease with each year, and having a younger biological age decreases these risks.

Your OMICm Biological Age can represent an increase or decrease risk of Death, Cancer, Heart Disease, Stroke, Type 2 Diabetes, COPD, and Depression.

-28% Disease Risk — *Reflects your current risk. A -28% score means that your **risk** is 28% **lower** compared to people of your same chronological age.*

47% Disease Risk — *Reflects your current risk. A 47% score means that your **risk** is 47% **higher** compared to people of your same chronological age.*

31% — *Reflects your potential risk score based on potential changes to your biological age.*

DEATH

-3 YEARS	-1 YEAR	Disease Risk	+1 YEAR	+3 YEARS
-56.97%	-47.18%	-41.48%	-35.16%	-20.4%

CANCER

-3 YEARS	-1 YEAR	Disease Risk	+1 YEAR	+3 YEARS
-56.97%	-47.18%	-41.48%	-35.16%	-20.4%

STROKE

-3 YEARS	-1 YEAR	Disease Risk	+1 YEAR	+3 YEARS
-56.97%	-47.18%	-41.48%	-35.16%	-20.4%

RESULTS CONTINUED ON NEXT PAGE

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HEART DISEASE

TYPE 2 DIABETES

COPD

DEPRESSION

- END OF DISEASE RISK RESULTS -

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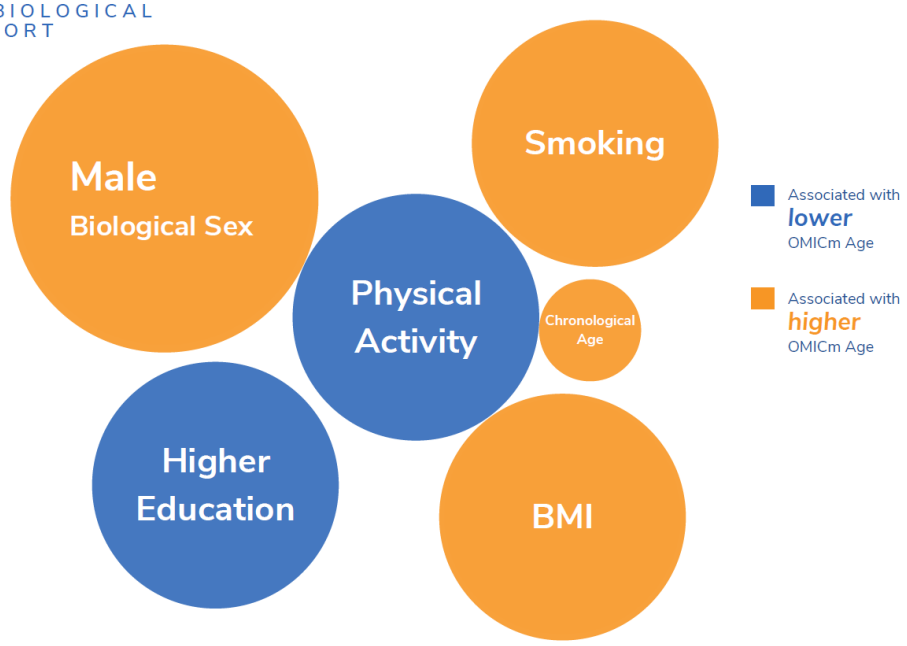
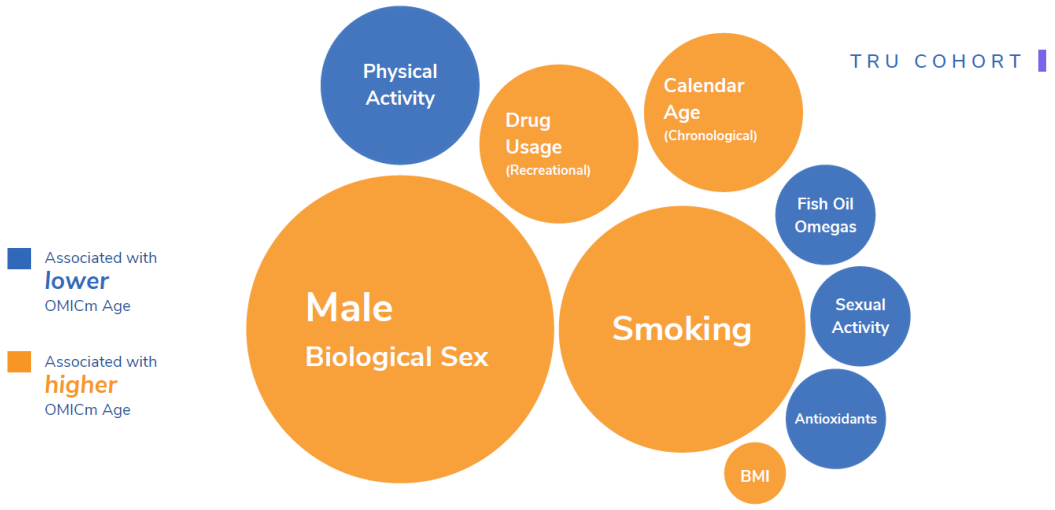
In the chart below, you can see some of the top factors that contribute to an increase (yellow) or decrease **(blue)** of OMICm Age.

While some influences like sex and chronological age are innate and unchangeable, **most contributing factors like smoking and physical activity can be modified.** It is important to note that an influence, or association, is not necessarily a cause. The chart below shows **research-backed associations with a higher or lower biological age.** These factors may or may not be direct causes, however, strong age-related trends have been distinguished.

HARVARD BIOLOGICAL AGING COHORT



TRU COHORT



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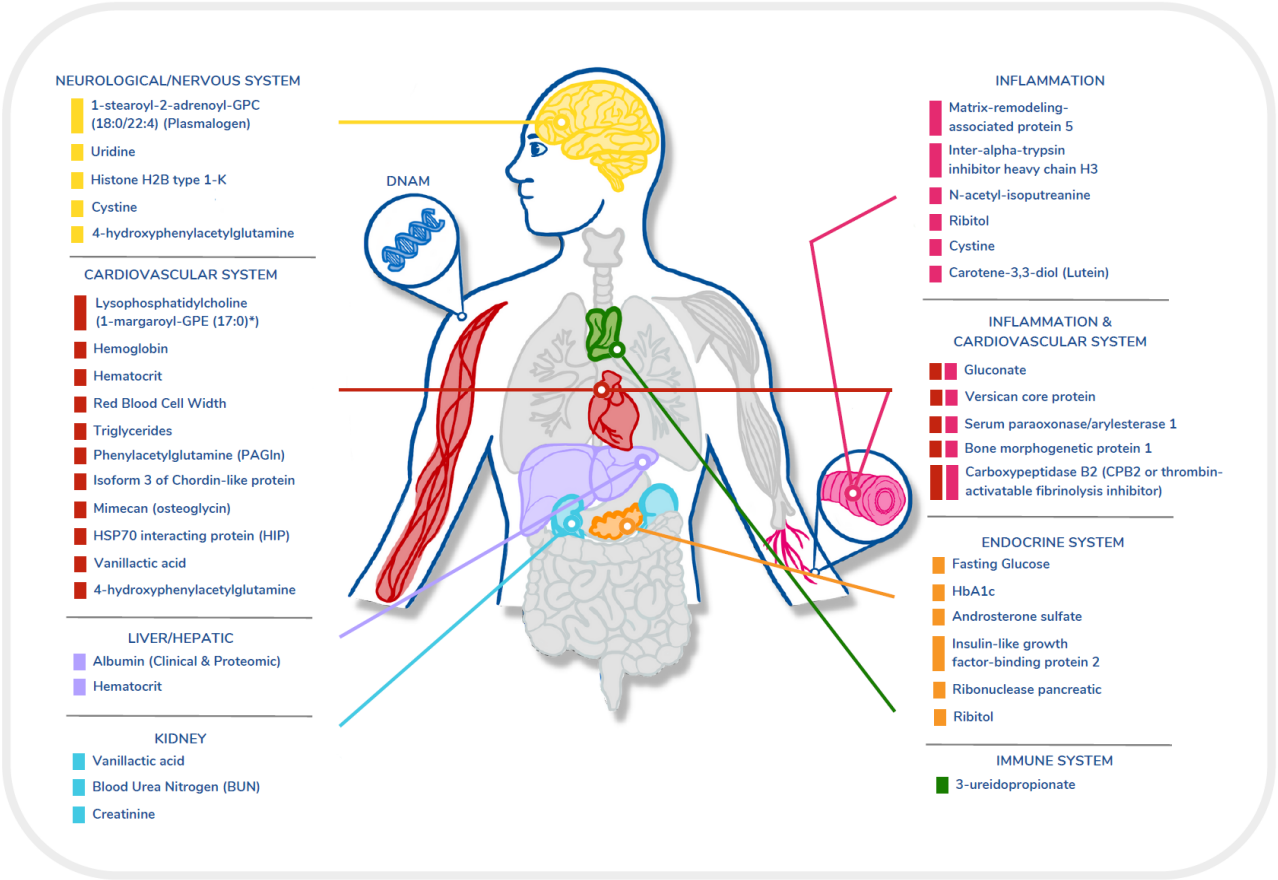
THE EPIGENETIC BIOMARKER PROXIES DRIVING YOUR BIOLOGICAL AGE

We use epigenetic biomarker proxies (EBPs) to predict genomics, transcriptomics, proteomics, and metabolomics sum values that are positive for your aging, and some that are negative for your aging. In the graph below you will see the factors contributing to your aging the most. If a bar is above zero, it's increasing your OMICm Age, if below zero, it is decreasing your OMICm Age.

BODY SYSTEMS CONTRIBUTING TO THE DEVELOPMENT OF OMICAGE THROUGH OMICS



Neurological/Nervous System | Cardiovascular system | DNAm | Liver/Hepatic

Immune System | Kidney | Endocrine System | Inflammation

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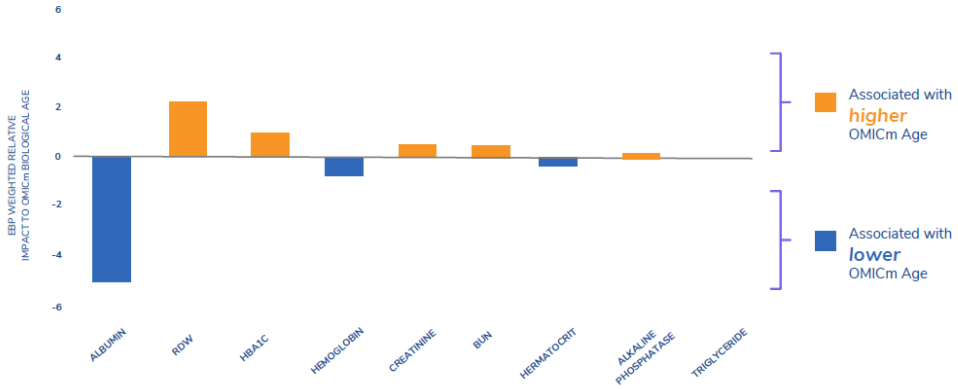
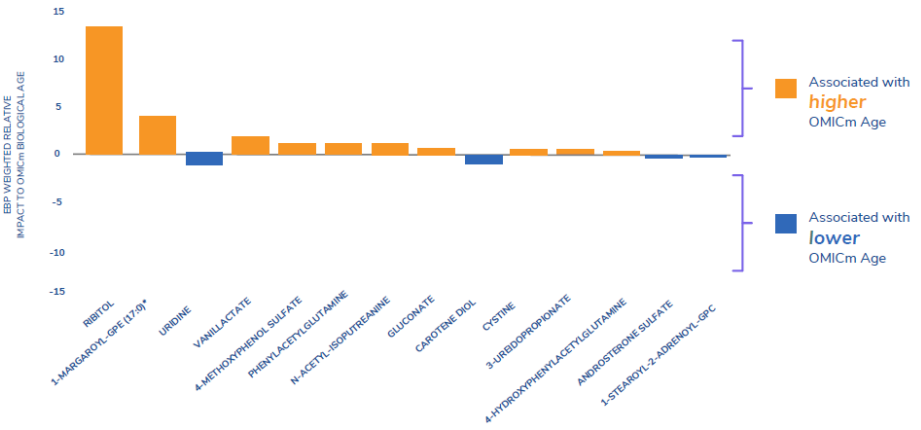
CLINICAL FACTORS

Your Clinical Epigenetic Biomarker Proxies (EBP)



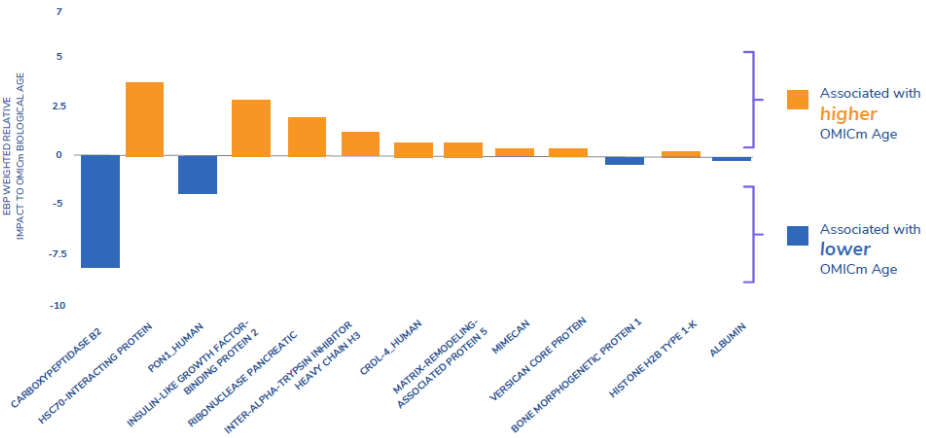
METABOLITES

Your Metabolites Epigenetic Biomarker Proxies (EBP)



PROTEINS

Your Proteomics Epigenetic Biomarker Proxies (EBP)



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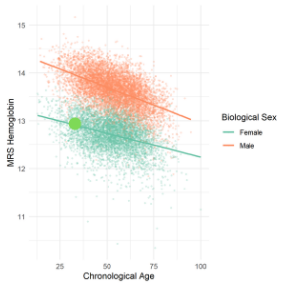
CLINICAL RESULTS
EXPANDED

Hemoglobin

HIGHER RATES ASSOCIATED WITH IMPROVED OMIC AGE

13 g/dl

Your **Hemoglobin** is higher than 2% of the population at your same calendar age and sex.

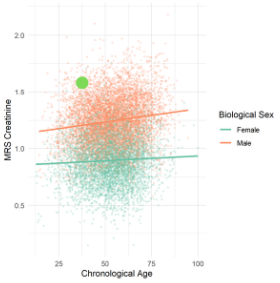


Creatinine

LOWER RATES ASSOCIATED WITH IMPROVED OMIC AGE

1.6 mg/dL

Your **Creatinine** is higher than 95% of the population at your same calendar age and sex.

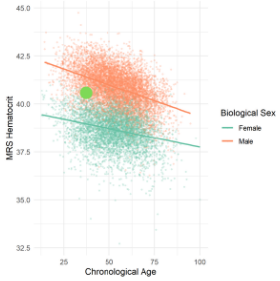


Hematocrit

HIGHER RATES ASSOCIATED WITH IMPROVED OMIC AGE

41 L/L

Your **Hematocrit** is higher than 20% of the population at your same calendar age and sex.

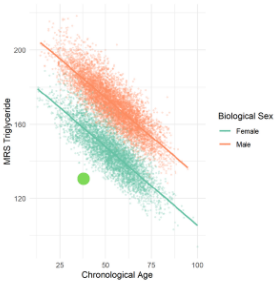


Triglycerides

HIGHER RATES ASSOCIATED WITH IMPROVED OMIC AGE

138 mmol/L

Your **Triglycerides** is higher than 0% of the population at your same calendar age and sex.



Alkaline Phosphatase (ALP)

LOWER RATES ASSOCIATED WITH IMPROVED OMIC AGE

71 U/L

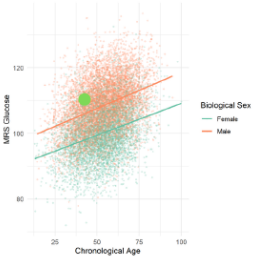
Your **Alkaline Phosphatase (ALP)** is higher than 5% of the population at your same calendar age and sex.

Fasting Glucose

LOWER RATES ASSOCIATED WITH IMPROVED OMIC AGE

114 mmol/L or in mg/dL

Your **Fasting Glucose** is higher than 60% of the population at your same calendar age and sex.

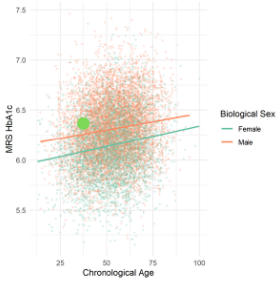


HbA1c

LOWER RATES ASSOCIATED WITH IMPROVED OMIC AGE

6.3 %

Your **HbA1c** is higher than 55% of the population at your same calendar age and sex.

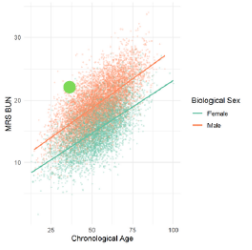


Blood Urea Nitrogen (BUN)

LOWER RATES ASSOCIATED WITH IMPROVED OMIC AGE

22 mg/dLor in mmol/L

Your **Blood Urea Nitrogen (BUN)** is higher than 90% of the population at your same calendar age and sex.



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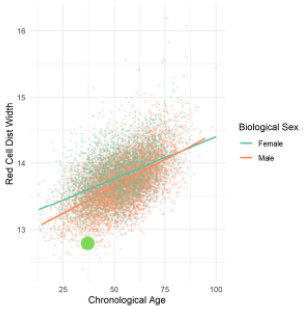
Red Blood Cell Width

LOWER RATES ASSOCIATED WITH IMPROVED OMIC AGE

12 fL

Your **Red Blood Cell Width** is higher than 5% of the population at your same calendar age and sex.

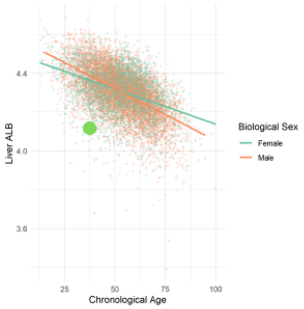


Albumin (Clinical)

HIGHER RATES ASSOCIATED WITH IMPROVED OMIC AGE

4.2 g/dL

Your **Albumin (Clinical)** is higher than 10% of the population at your same calendar age and sex.



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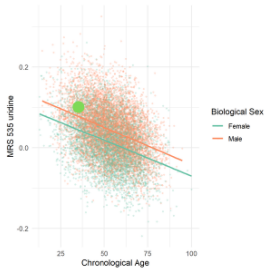
METABOLITE RESULTS
EXPANDED

Uridine

HIGHER RATES ASSOCIATED WITH IMPROVED OMIC AGE

0.15

Your **Uridine** is higher than **51%** of the population at your same calendar age and sex.

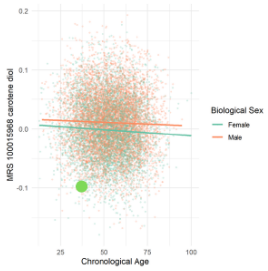


Carotene-3,3-diol (Lutein)

HIGHER RATES ASSOCIATED WITH IMPROVED OMIC AGE

-0.1

Your **Carotene-3,3-diol (Lutein)** is higher than **20%** of the population at your same calendar age and sex.

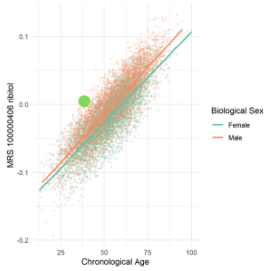


Ribitol

LOWER RATES ASSOCIATED WITH IMPROVED OMIC AGE

0.0

Your **Ribitol** is higher than **95%** of the population at your same calendar age and sex.

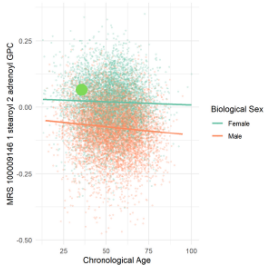


1-stearoyl-2-adrenoyl-GPC (18:0/22:4) (Plasmalogen)

HIGHER RATES ASSOCIATED WITH IMPROVED OMIC AGE

0.09

Your **1-stearoyl-2-adrenoyl-GPC (18:0/22:4) (Plasmalogen)** is higher than **70%** of the population at your same calendar age and sex.

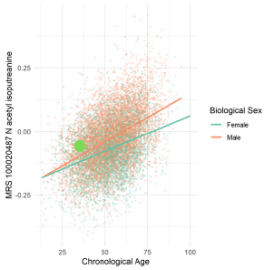


N-acetyl-isoputreanine

LOWER RATES ASSOCIATED WITH IMPROVED OMIC AGE

-0.05

Your **N-acetyl-isoputreanine** is **55%** higher compared to people of your same calendar age and sex.

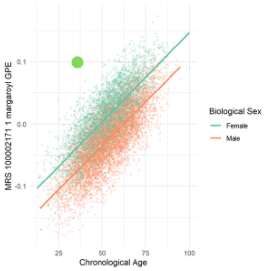


Lysophosphatidylcholine (1-margaroyl-GPE (17:0)*)

LOWER RATES ASSOCIATED WITH IMPROVED OMIC AGE

0.1

Your **Lysophosphatidylcholine (1-margaroyl-GPE (17:0)*)** is higher than **100%** of the population at your same calendar age and sex.

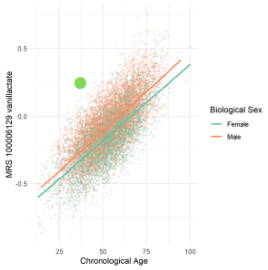


Vanillactate acid

LOWER RATES ASSOCIATED WITH IMPROVED OMIC AGE

0.3

Your **Vanillactate acid** is higher than **100%** of the population at your same calendar age and sex.

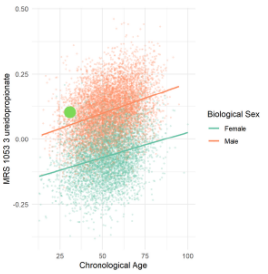


3-ureidopropionate

LOWER RATES ASSOCIATED WITH IMPROVED OMIC AGE

0.8

Your **3-ureidopropionate** is higher than **57%** of the population at your same calendar age and sex.



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PATIENT: XXXXXXXXXXXXXXX
TEST NUMBER: G-NL-XXXXXXX
GENDER: XX
AGE: XX

COLLECTED: 23-Mar-2023
RECEIVED: 01-Mar-2023
TESTED: 01-Mar-2023

TEST REF: GNL-NL-XXXXX
PRACTITIONER:
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XXXXXXXXXXXXXXXXXXX

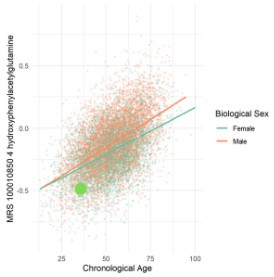
TEST NAME: OMICm Age Report

4-hydroxyphenylacetylglutamine

LOWER RATES ASSOCIATED WITH IMPROVED OMIC AGE

-0.5

Your **4-hydroxyphenylacetylglutamine** is higher than **32%** of the population at your same calendar age and sex.

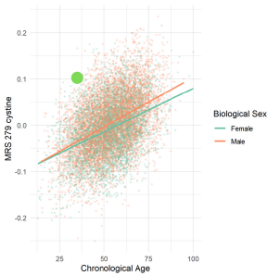


Cystine

LOWER RATES ASSOCIATED WITH IMPROVED OMIC AGE

0.1

Your **Cystine** is higher than **91%** of the population at your same calendar age and sex.

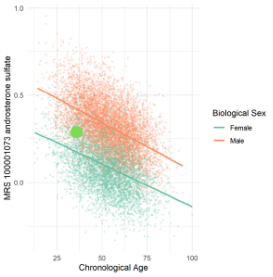


Androsterone Sulfate

HIGHER RATES ASSOCIATED WITH IMPROVED OMIC AGE

0.2

Your **Androsterone Sulfate** is higher than **15%** of the population at your same calendar age and sex.



Gluconate

LOWER RATES ASSOCIATED WITH IMPROVED OMIC AGE

0.3

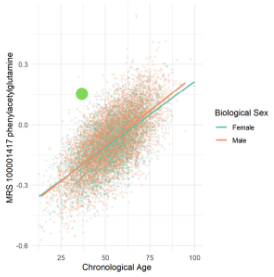
Your **Gluconate** is higher than **93%** of the population at your same calendar age and sex.

Phenylacetylglutamine (PAGln)

LOWER RATES ASSOCIATED WITH IMPROVED OMIC AGE

0.2

Your **Phenylacetylglutamine (PAGln)** is higher than **98%** of the population at your same calendar age and sex.

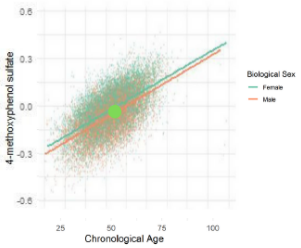


4-methoxyphenol sulfate

LOWER RATES ASSOCIATED WITH IMPROVED OMIC AGE

0.0

Your **4-methoxyphenol sulfate** is higher than **90%** of the population at your same calendar age and sex.



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SSSSSSSSSSS
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TEST NAME: OMICm Age Report

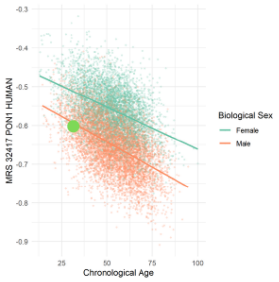
PROTEIN RESULTS
EXPANDED

Serum paraoxonase/ arylesterase

HIGHER RATES ASSOCIATED WITH IMPROVED OMIC AGE

-0.6

Your **Serum paraoxonase/ arylesterase** is higher than 3% of the population at your same calendar age and sex.

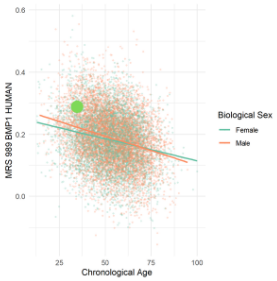


Bone morphogenetic protein 1

HIGHER RATES ASSOCIATED WITH IMPROVED OMIC AGE

0.1

Your **Bone morphogenetic protein 1** is higher than 35% of the population at your same calendar age and sex.

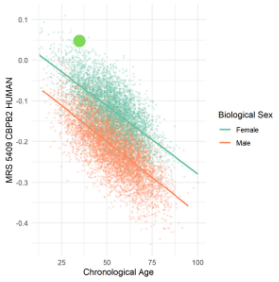


Carboxypeptidase B2 (CPB2 or thrombin-activatable fibrinolysis inhibitor)

HIGHER RATES ASSOCIATED WITH IMPROVED OMIC AGE

0.05

Your **Carboxypeptidase B2 (CPB2 or thrombin-activatable fibrinolysis inhibitor)** is higher than 100% of the population at your same calendar age and sex.

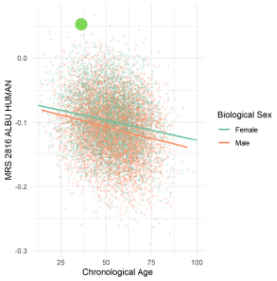


Albumin

HIGHER RATES ASSOCIATED WITH IMPROVED OMIC AGE

0.1

Your **Albumin** is higher than 100% of the population at your same calendar age and sex.

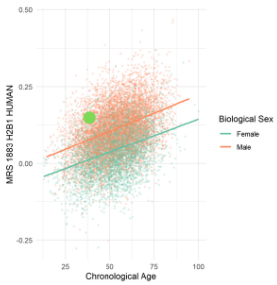


Histone H2B type 1-K

LOWER RATES ASSOCIATED WITH IMPROVED OMIC AGE

0.20

Your **Histone H2B type 1-K** is higher than 40% of the population at your same calendar age and sex.

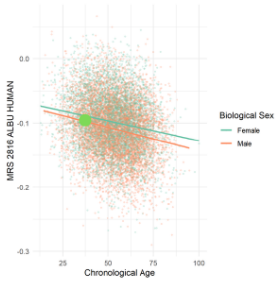


Versican core protein

LOWER RATES ASSOCIATED WITH IMPROVED OMIC AGE

-0.1

Your **Versican core protein** is higher than 1% of the population at your same calendar age and sex.



Insulin-like growth factor-binding protein 2

LOWER RATES ASSOCIATED WITH IMPROVED OMIC AGE

73

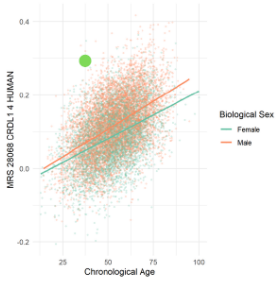
Your Insulin-like growth factor-binding protein 2 is higher than 5% of the population at your same calendar age and sex.

Matrix-remodeling-associated protein 5

LOWER RATES ASSOCIATED WITH IMPROVED OMIC AGE

0.3

Your **Matrix-remodeling-associated protein 5** is higher than 100% of the population at your same calendar age and sex.



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PATIENT: XXXXXXXXXXXXXX

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SSSSSSSSSSS

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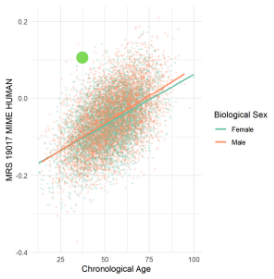
TEST NAME: OMICm Age Report

Mimecan

LOWER RATES ASSOCIATED WITH IMPROVED OMIC AGE

-0.1

Your **Mimecan** is higher than 100% of the population at your same calendar age and sex.

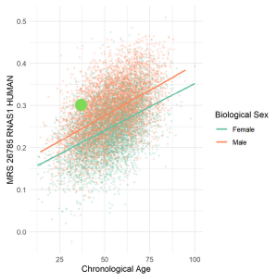


Ribonuclease pancreatic

LOWER RATES ASSOCIATED WITH IMPROVED OMIC AGE

0.3

Your **Ribonuclease pancreatic** is higher than 50% of the population at your same calendar age and sex.

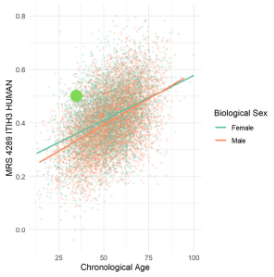


Inter-alpha-trypsin inhibitor heavy chain H3

LOWER RATES ASSOCIATED WITH IMPROVED OMIC AGE

0.5

Your **Inter-alpha-trypsin inhibitor heavy chain H3** is higher than 40% of the population at your same calendar age and sex.

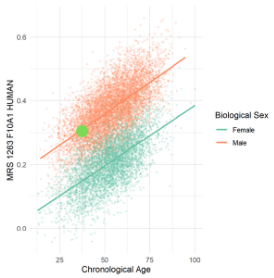


HSP70 interacting protein (HIP)

LOWER RATES ASSOCIATED WITH IMPROVED OMIC AGE

0.3

Your **HSP70 interacting protein (HIP)** is higher than 90% of the population at your same calendar age and sex.

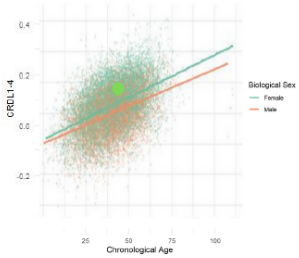


CRDL 1-4 protein

LOWER RATES ASSOCIATED WITH IMPROVED OMIC AGE

0.2

Your **CRDL 1-4 protein** is higher than 15% of the population at your same calendar age and sex.



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VALUES FACTORED IN OMICm AGE

Biomarker definitions.

Hemoglobin
Red blood cells contain the protein hemoglobin, which transports oxygen. How much hemoglobin is in your blood is determined by the hemoglobin test. The most significant part of red blood cells is hemoglobin. It is made up of heme, a protein that binds oxygen.

Hematocrit
The volume percentage of red blood cells in blood is assessed as part of a blood test and is referred to by a number of other names. Red blood cell quantity and size determine this measurement.

Creatinine
Creatinine is a waste product that comes from the normal wear and tear on muscles of the body. Everyone has creatinine in their bloodstream. However, amounts vary based on age, body size, race, and gender.

Triglycerides
Triglycerides are a type of fat, called lipid, that circulate in your blood. They are the most common type of fat in your body. Triglycerides come from foods, especially butter, oils, and other fats. Unused calories are stored as triglycerides in fat cells. When your body needs energy, it releases the triglycerides. High triglyceride levels in your blood can raise your risk of heart disease and stroke.

Alkaline Phosphatase (ALP)
Your body contains an enzyme called alkaline phosphatase (ALP). One of the tests in a full metabolic panel, ALP blood tests evaluate the amount of ALP produced by your liver and bones in your blood. High blood levels of ALP may be a sign of liver disease or specific bone problems.

Fasting Glucose
The primary sugar present in your blood is glucose. It serves as the main energy source for your body. It originates in the food you consume. The majority of that meal is converted by your body into glucose, which is then released into your bloodstream. Your pancreas releases insulin when your blood glucose levels rise.

HbA1c
The A1C test, sometimes called a HbA1c test or a hemoglobin A1C test, is a quick blood test that gauges your average blood sugar levels over the previous three months. The primary test to assist you and your healthcare team in managing your diabetes, it is one of the often utilized tests to diagnose prediabetes and diabetes

Blood Urea Nitrogen (BUN)
The amount of urea nitrogen in your blood is determined by a blood urea nitrogen (BUN) test. When your liver breaks down protein, urea nitrogen is produced as a waste product. Your blood carries it, your kidneys filter it out, and your urine excretes it from your body.

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TEST NAME: OMICm Age Report

Red Blood Cell Width

The measure of the difference in the volume and size of your red blood cells (erythrocytes). The volume of red blood cells varies even in healthy blood, with an average volume of 80–100 femtoliters. However, some illnesses result in a markedly greater fluctuation in cell size. Greater size variation is indicated by higher RDW values. RDW-CV in human red blood cells typically falls between 11.5 and 15.4%.

Albumin (Clinical)

The protein albumin is produced by your liver. Albumin enters your bloodstream and aids in preventing fluid from seeping into other tissues from your blood vessels. It also transports vitamins, enzymes, and hormones throughout the body. If your blood doesn't contain enough albumin, fluid may leak out and accumulate in your lungs, abdomen, or other areas of your body. Low albumin levels may indicate liver, renal, or other types of illness. Dehydration may be indicated by high levels

Uridine

Uridine is an important building block used in the creation of RNA. It may support brain health, synaptic connections, and cholinergic function. A 2018 study identified it as one of 12 metabolites predictive of living over the age of 85 in women. Other studies have also shown that it is linked to all-cause mortality. Lower uridine levels in Alzheimer's disease (AD) were associated with clinical progression.
In some studies, it has been identified as a factor that promotes human stem cell activity and enhanced regeneration in multiple tissues across multiple mammal species.

Carotene-3,3-diol (Lutein)

Carotene-3,3-diol is one of 600 known naturally occurring carotenoids. It is synthesized only by plants and is found in high quantities in green leafy vegetables such as spinach, kale, and yellow carrots. Some studies have shown that supplementation can help improve cognitive function and eye health. A large meta-analysis involving 71 published papers and representing more than 387,000 individuals showed that people with higher lutein intake, or higher blood concentrations of lutein, have a reduced risk of coronary heart disease, stroke, and metabolic syndrome. Lutein provides such wide-reaching effects because it protects tissues from oxidative stress and inflammation—two factors that play a significant role in cardiovascular and metabolic diseases.

Ribitol

Ribitol is a pentose alcohol formed by the reduction of ribose. Ribitol forms part of the chemical structure of riboflavin and flavin mononucleotide (FMN). It is also a metabolic end product formed by reducing ribose in human fibroblasts and erythrocytes. It has been a blood-based biomarker of diabetic retinopathy and biological process clustering studies have shown it to be associated with insulin secretion and diabetes pathways which are highly related to mortality. Higher concentrations of similar metabolites like ribonic acid have also been linked to CKD.

1-stearoyl-2-adrenoyl-GPC (18:0/22:4) (Plasmalogen)

This is a choline ether phospholipid (ePC) that is present in human serum or plasma. Decreases in ether phospholipids (plasmalogens) in serum (plasma) have been reported in several diseases such as Alzheimer's disease, Parkinson's disease, metabolic syndrome, and schizophrenia.

N-acetyl-isoputreanine

Isoputreanine belongs to the class of organic compounds known as gamma amino acids and derivatives.

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Gluconate

Gluconic acid occurs naturally in fruit, honey, and wine. It has been identified as a lifestyle-related biomarker that may be a target to reduce stroke risk in Black adults. Higher levels of gluconic acid in the blood were associated with high blood pressure and increased risk of ischemic stroke among Black adults when compared to white adults. It also may be considered as a dietary-related oxidative stress marker due to its availability in food, potentially produced by the gut microbiome, and related to diseases with oxidative stress. Of the 162 metabolites measured in one study, elevated levels of gluconic acid were found in Black adults who had high blood pressure but not their white peers with high blood pressure. Black adults with the highest gluconic acid levels were 86% more likely to have high blood pressure. Black adults with the highest gluconic acid levels had a 53% increased risk of ischemic stroke. No such association was found for white participants. Gluconic acid accounted for 25% of the association between high blood pressure and stroke among Black adults. After adjusting for multiple factors, a higher level of gluconic acid was associated with a Southern diet (foods high in added fats, fried foods, processed meats, and sugary drinks), and a lack of exercise.

Phenylacetylglutamine (PAGln)

Phenylacetylglutamine (PAGln) is a gut microbiota-derived metabolite that may induce cardiovascular events by activating platelets and increasing the risk of thrombosis. The highly-nitrogenous compound is most commonly encountered in human subjects with urea cycle disorders. These conditions, such as uremia or hyperammonemia, tend to cause high levels of nitrogen in the form of ammonia in the blood. It also has been used as a biomarker of acute stroke. High levels of phenylacetylglutamine in the urine following metabolism by the gut microbiota may also indicate early renal decline associated with kidney dysfunction and chronic kidney disease (CKD). In CKD, phenylacetylglutamine is considered a uremic toxin which is taken up, circulated, and retained in the blood after microbial fermentation of certain proteins and amino acids in the gut. Blood serum levels of phenylacetylglutamine in CKD are used as a mortality determinant. Blood plasma levels of phenylacetylglutamine increase with exposure to cigarette smoke, in patients with ischemic heart failure, with cardiovascular risk or hypertension, in patients with disease, and in patients with type 2 diabetes.

Serum paraoxonase/arylesterase

Serum paraoxonase and arylesterase 1 (PON1) is an enzyme encoded by the PON1 gene. Serum PON1 is secreted mainly by the liver, although local synthesis occurs in several tissues and PON1 protein is found in almost all tissues. PON1 is also a major anti-atherosclerotic component of HDL Cholesterol (good cholesterol). The PON1 gene is activated by PPAR-γ, which increases synthesis and release of paraoxonase 1 enzyme from the liver, reducing atherosclerosis. In addition to protecting against exposure to some organophosphorus (OP) pesticides by hydrolyzing their toxic oxon metabolites, PON1 is important in protecting against vascular disease by metabolizing oxidized lipids. Circulating plasma levels of leptin, hs-CRP, and IL-6 were significantly non-linearly associated with arylesterase activity. Leptin levels were also significantly associated with paraoxonase activity independently from confounding factors, including high-density lipoprotein (HDL) cholesterol. With increasing levels of inflammatory parameters, arylesterase, and paraoxonase activities increased; This suggests that in persons with very high levels of inflammation, PON1 activity may be impaired, a fact that might subsequently be accompanied by a higher risk for cardiometabolic diseases.

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Lysophosphatidylcholine (1-margaroyl-GPE (17:0)*)

Lysophosphatidylcholine (LPC) is increasingly recognized as a key marker/factor positively associated with cardiovascular and neurodegenerative diseases. LPC is mainly derived from the turnover of phosphatidylcholine (PC) in circulation by phospholipase A2 (PLA2). In the presence of Acyl-CoA, lysophosphatidylcholine acyltransferase (LPCAT) converts LPC to PC. However, overexpression or enhanced activity of PLA2 increases the LPC content in modified low-density lipoprotein (LDL) and oxidized LDL, which play significant roles in the development of atherosclerotic plaques and endothelial dysfunction. Hydrolysis of LPC by autotaxin, an enzyme with lysophospholipase D activity, generates lysophosphatidic acid, which is highly associated with cancers

Vanillactic acid

Vanillactic acid, also referred to as vanillactate or VLA falls within the category of organic substances termed phenylpropanoic acids. Phenylpropanoic acids are compounds characterized by a structure that incorporates a benzene ring connected to propanoic acid. Vanillactic acid possesses potential toxicity and has been associated with inborn metabolic disorders, including aromatic l-amino acid decarboxylase deficiency.

3-ureidopropionate

Ureidopropionic acid is essentially a urea derivative of beta-alanine. High levels of ureidopropionic acid are found in individuals with beta-ureidopropionase (UP) deficiency. It has been identified as one of the major metabolites Metabolites Associated With the Risk of Developing Mobility Disability This can also be present in Albuminuria. Albuminuria is an indicator of sub-clinical organ damage and a marker of cardiovascular risk and renal disease.

4-hydroxyphenylacetylglutamine

4-Hydroxyphenylacetylglutamic acid belongs to the class of organic compounds known as glutamic acid and derivatives. This is a metabolite which is upregulated in cystic fibrosis. It also has been suggested to be a novel biomarker of type 2 diabetes with polyneuropathy and also has shown a link to systolic blood pressure in women.

Cystine

Cysteine (Cys) the primary sulfur-containing amino acid (SAA) is a semiessential amino acid (AA) because it can be obtained from the diet or produced from methionine degradation via the transsulfuration pathway. Cystine is common in many foods such as eggs, meat, dairy products, and whole grains as well as skin, horns, and hair. Within the body, cysteine catabolic pathways are sources of the synthesis of coenzyme A, glutathione, taurine, and oxidized and reduced inorganic sulfur. Cysteine is more easily absorbed by the body than cystine, so most supplements contain cysteine rather than cystine.

Androsterone Sulfate

Androsterone sulfate (Andros-S) is the most abundant 5-alpha-reduced androgen metabolite in serum. This means higher testosterone levels generally yield higher versions of this metabolite.

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TEST NAME: OMICm Age Report

Bone morphogenetic protein 1

Bone morphogenetic protein 1, also known as BMP1, is a protein that in humans is encoded by the BMP1 gene. It induces bone and cartilage development. BMP-1 stimulates the conversion of newly secreted proapo A1 to its phospholipid- (PL-) binding form. In this way, it promotes the formation of functional HDL and reverse cholesterol transport. Higher levels of inflammation have been shown to be associated with a decrease in BMP1 and therefore APOA1 and thus it has been suggested as a marker for inflammation and cardiovascular disease risk

Carboxypeptidase B2 (CPB2 or thrombin-activatable fibrinolysis inhibitor)

CPB2 is synthesized by the liver and circulates in the plasma as a plasminogen-bound zymogen. When it is activated by the thrombin/thrombomodulin complex, CPB2 exhibits carboxypeptidase activity. Activated CPB2 reduces fibrinolysis by removing the fibrin C-terminal residues that are important for the binding and activation of plasminogen. Lower CPB2 has been suggested as a biomarker of peripheral artery disease. This could be a biomarker of chronic hepatitis and thrombotic risk. Profound hypercoagulability seems to be mediated by the overexpression of plasminogen activator inhibitor 1 (PAI-1) and CBP2.

Albumin

The protein albumin is produced by your liver. Albumin enters your bloodstream and aids in preventing fluid from seeping into other tissues from your blood vessels. It also transports vitamins, enzymes, and hormones throughout the body. If your blood doesn't contain enough albumin, fluid may leak out and accumulate in your lungs, abdomen, or other areas of your body. Low albumin levels may indicate liver, renal, or other types of illness. Dehydration may be indicated by high levels.

Histone H2B type 1-K

Histone H2B type 1-K is a core component of the nucleosome or the proteins which wrap and control the expression of DNA. Nucleosomes wrap and compact DNA into chromatin, limiting DNA accessibility to the cellular machinery which requires DNA as a template. Histones thereby play a central role in transcription regulation, DNA repair, DNA replication, and chromosomal stability. DNA accessibility is regulated via a complex set of post-translational modifications of histones, also called histone code, and nucleosome remodeling. H2B Type 1-K has been shown to accumulate in senescent Fibroblasts with Persistent DNA Damage.

Versican core protein

Versican is an extracellular matrix protein that has been shown to increase during inflammation in a number of different diseases such as cardiovascular and lung disease, autoimmune diseases, and several different cancers. Versican interacts with inflammatory cells either indirectly via hyaluronan or directly via receptors such as CD44, P-selectin glycoprotein ligand-1 (PSGL-1), and toll-like receptors (TLRs) present on the surface of immune and non-immune cells. These interactions activate signaling pathways that promote the synthesis and secretion of inflammatory cytokines such as TNFα, IL-6, and NFκB.

Insulin-like growth factor-binding protein 2

IGFBP-2 is an insulin-like growth factor (IGF) binding protein (IGFBPs) that modulates IGF-I's actions. It plays an important role in the regulation of several cellular processes. IGFBP-2 is the second most abundant IGFBP and is expressed in several tissues, including blood vessels and the skeleton. IGFBP-2 can prevent IGF-I binding to its receptor, but it also modulates cellular functions independently of IGF-I binding It has been suggested to be a biomarker of metabolic disease and diabetes.

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TEST NAME: OMICm Age Report

Matrix-remodeling-associated protein 5

This gene encodes one of the matrix-remodeling associated proteins. MMPs are capable of degrading all kinds of extracellular matrix proteins but also can process a number of bioactive molecules. They are known to be involved in the cleavage of cell surface receptors, the release of apoptotic ligands, and chemokine/cytokine inactivation. MMPs are also thought to play a major role in cell behaviors such as cell proliferation, migration (adhesion/dispersion), differentiation, angiogenesis, apoptosis, and host defense.

Mimecan

Mimecan, also known as osteoglycin, is an ECM component. Mimecan affects several biological processes including the regulation of collagen fibrillogenesis and angiogenesis. Mimecan is expressed in atherosclerotic tissue and Human coronary arteries and is downregulated in intimal vascular smooth muscle cells (VSCMs). Studies have shown mimecan is associated with a vulnerable plaque phenotype, possibly regulated by plaque inflammation, and thus might predict future cardiovascular death and arterial stiffness.

Ribonuclease pancreatic

Pancreatic ribonuclease also known as ribonuclease A (RNase A) or ribonuclease 1 (RNase1) is an enzyme that catalyzes the breakdown of RNA and plays a role in the digestion of RNA in vertebrate species. RNase is present in much lower amounts in humans than in other species and may account for only 0.5 to 1% of pancreatic enzymes. Although only a few studies exist, pancreatic RNase in all species appears to break down dietary nucleic acid in the gut lumen to nucleotides. Not much is described about this protein as a biomarker, however, highway levels have been linked to more aggressive cancers.

Inter-alpha-trypsin inhibitor heavy chain H3

Inter-alpha (globulin) inhibitor 3 (ITIH3), one of the constituents of plasma serine protease inhibitors, has been shown to be related to the proinflammatory process (Fries and Kaczmarczyk 2003). This complex, named pre-alpha trypsin inhibitor (Pαl) is synthesized by hepatocytes and released to the blood vessel upon stimulation of the proinflammatory cytokines (tumor necrosis factor or interleukin-1). Then, ITIH3 makes a complex with the locally synthesized hyaluronan (HA) and interacts with inflammatory cells (Fries and Kaczmarczyk 2003). - ITIH3-HA complex has been reported to be involved in inflammatory diseases, including rheumatoid arthritis and inflammatory bowel diseases (Zhuo et al. 2004). Variants with this protein have also been shown to be associated with psychiatric diseases.

HSP70 interacting protein (HIP)

HSP90 interacting protein is a co-chaperone heat shock protein that helps with appropriate protein folding. One aspect of this protein, C terminus of Hsc70-interacting protein (CHIP), frequently promotes ubiquitination and degradation of several proteins. The impact of upregulated CHIP has not been well studied. CHIP has been reported to play an important role in preventing cell apoptosis. CHIP also displays a critical cardioprotective effect in response to ischemia/reperfusion injury. CHIP is a negative regulator of FoxO1 activity through ubiquitin-mediated degradation, and inhibition of CHIP has been postulated to serve as a potential therapeutic target for reducing proliferative arterial diseases.

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EDUCATIONAL GRAPHS

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PATIENT: XXXXXXXXXXXXXX			TEST REF: GNL-NL-XXXXX
TEST NUMBER: G-NL-XXXXXXX	COLLECTED: 23-Mar-2023		PRACTITIONER: SSSSSSSSSSS
GENDER: XX	RECEIVED: 01-Mar-2023		
AGE: XX	TESTED: 01-Mar-2023		XXXXXXXXXXXXXXXXXX

TEST NAME: DunedinPACE Report

TRUAGE BY TRUDIAGNOSTIC

DunedinPACE

This report is able to tell you how many biological years you are aging per year at the precise moment.
This algorithm was created by Duke and Columbia via a longitudinal study.

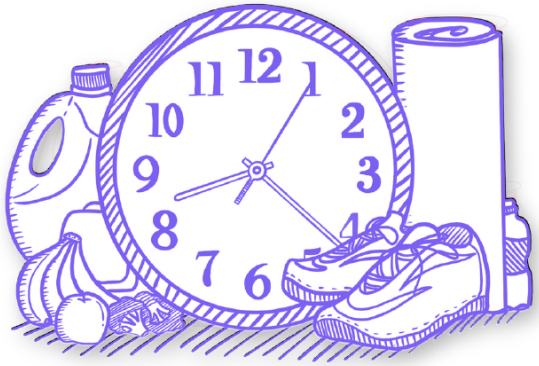
Developed By TruDiagnostic's Bioinformatics & Research Department

UNDERSTANDING

your pace of biological aging.

Methylation-based biological aging clocks changed the way we look at aging and preventive medicine!

Aging is the number one risk factor for most chronic diseases. Unfortunately, traditional determinants of age (the number of years since birth) don't always match up with how each individual ages. Some people in their 70s look and feel like they are 50, and then there are some 70-year-olds that look like they could be 90. **This is called phenotypic variation, and as a result, people have been searching for objective markers to measure the aging process.** Thankfully, a highly accurate one was created by measuring epigenetic biomarkers.



Having an objective biological age measurement has massive implications for preventative health and future investigations. However, if we can combine this with an instantaneous rate of aging, we can learn even more about our aging process, our individual aging biology, and the interventions for better preventative health when we combine these two metrics.

JANE DOE | ID # ABC123
COLLECTED: 06/01/2020 | REPORTED: 07/01/2020

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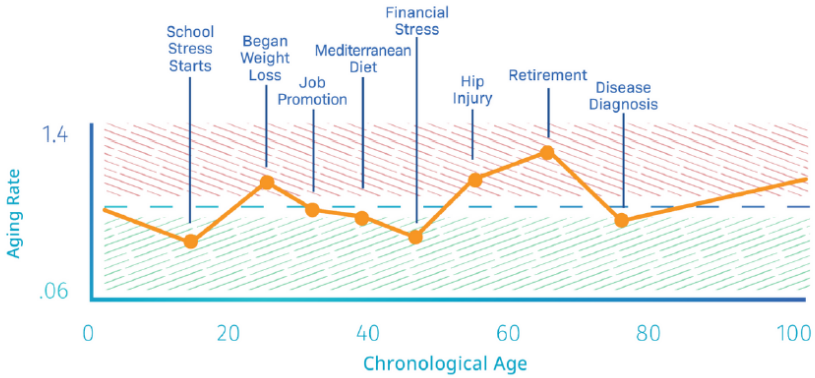
TEST NAME: Alcohol Consumption Report

UNDERSTANDING

Your rate of aging versus your body's biological age.

Quantifying one's rate of aging versus biological age is like having a speedometer of aging instead of determining age at a fixed moment in time. Biological age is a great metric, but it doesn't compare past history from current influences on the methylome.



There are many external factors that influence one's pace of aging. The above image is a graphical representation of potential influences on your pace of aging.

There are several cases where knowing both of these metrics can be useful. The best example to illustrate this might be the theoretical case of two identical twins; Twin 1 and Twin 2.

Twin 1 (40 years old chronologically) has lived a very healthy life by implementing proper nutrition, exercise, medications, and lifestyle patterns. On the other hand, Twin B (40 years old chronologically) hasn't lived a life full of similar, healthy habits. For instance, Twin B had a very stressful life in their twenties and early thirties and recently turned their life around. Now, both twins have the exact same lifestyle, nutrition, and exercise regimens along with having the same baseline DNA sequence.

If we only looked at their biological age, we would most likely see that Twin A has a lower biological age due to their consistent history of healthy habits. The same logic would lead us to expect that Twin B might have a worse biological age due to their health history. This might lead us to believe that Twin B is currently doing things in their life to lead to faster aging when in fact the lifestyles of each individual are exactly the same.

However, if we had a way to look at the instantaneous aging rate, we would be able to distinguish advanced aging, which occurred in the past, from the current rate of aging, which is regulated by ongoing lifestyle factors. Distinguishing these two points can also help us decide which lifestyle traits we should keep and which we should change.

Thankfully, due to researchers from Duke and Columbia, an algorithm that measures the pace of aging is already available for us to use.

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PATIENT: XXXXXXXXXXXXXXX
TEST NUMBER: G-NL-XXXXXXX
GENDER: XX
AGE: XX

COLLECTED: 23-Mar-2023
RECEIVED: 01-Mar-2023
TESTED: 01-Mar-2023

TEST REF: GNL-NL-XXXXX
PRACTITIONER:
SSSSSSSSSSS
XXXXXXXXXXXXXXXXXXX

TEST NAME: Alcohol Consumption Report

Your Results.

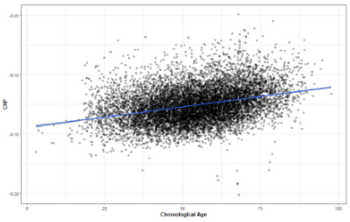
DunedinPACE Value

What Does Your Rate of Aging Mean?

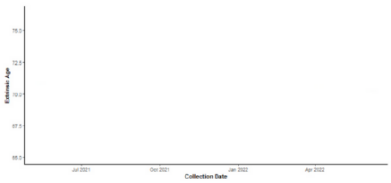
You want your rate of aging to be below one; this means you would have a slowed pace of aging. An average pace of aging would be a rate of 1 biological year for every chronological year aged.

DunedinPACE is associated with chronic disease morbidity and mortality. **Within 7 years from testing those with a faster pace of aging are at a 56% increased risk of death and a 54% increased risk for diagnosis of a chronic disease.**

Population



Changes Over Time



ALGORITHM	PATIENT DATA	MORBIDITY AND MORTALITY ASSOCIATIONS	RISK STATEMENT
DunedinPACE	X.XX Biological years per year	All-Cause Mortality (Beslsky et al., 2020)	If you are aging above a rate of 1.00, you would increase risk of death by 56% over the next 7 years.
		Chronic Disease (Beslsky et al., 2020)	If you are aging above a rate of 1.00, you would increase risk of chronic disease diagnosis by 54% over the next 7 years.

Mortality
Those with faster DunedinPACE levels, which indicates faster aging, at baseline were at increased risk of death having a hazard ratio of 1.29. The hazard ratio represents an instantaneous risk, it is the relationship between the instantaneous hazards between accelerated DunedinPACE and mortality.

Morbidity
Those with a faster DunedinPACE baseline were at an increased risk for a new chronic disease, putting them at a hazard ratio of 1.19. Individuals with faster DunedinPACE experienced higher levels of chronic disease morbidity, which was measured as the count of diagnosed diseases (hypertension, type-2 diabetes, cardiovascular disease, chronic obstructive pulmonary disease, chronic kidney disease, and cancer).

Accelerated Aging Influences
The pace of aging typically increases across much of the adult lifespan. A faster DunedinPACE is the result of a lifetime of accumulated stress to the methylome. Childhood exposure to poverty and victimization is associated with faster DunedinPACE. Adolescents who grew up in families of lower socioeconomic status and adolescents with exposure to multiple types of victimization exhibited faster DunedinPACE.

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TEST NAME: Alcohol Consumption Report

UNDERSTANDING

The study behind the algorithm.

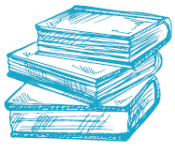
A team of researchers from Duke and Columbia were able to help create a test that could use blood samples to measure the pace of aging. This test is called the DunedinPACE and it can predict which people are at an increased risk of poor health, chronic disease, and more immediate death.

In order to develop this test, data on chemical changes to an individual's DNA, called DNA methylation, was collected from white blood cell samples from approximately 1,000 participants in a long-term health study known as "The Dunedin Study". Using the data obtained from this cohort the team developed an algorithm named "DunedinPACE". DundinPACE identified people with accelerated or slowed pace of aging based on a single blood test.

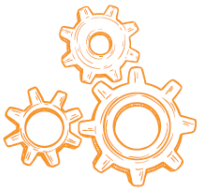
The researchers used a machine-learning technique called elastic-net regression to sort through data on more than 400,000 different DNA methylation marks to find the ones that related to the physiological changes that were captured in their Pace of Aging measure. The analysis pulled out a set of 173 methylation marks that, together, measured the pace of aging for individuals at one point in time.

Understanding Society

Analysis of chronological and biological age



PoAM Algorithm



Calerie

Analysis of intervention to slow biological aging

Dunedin Study

Analysis of age-45 functional decline

E-Risk Study

Analysis of early-life adversity

Normative Aging Study

Analysis of disease and mortality

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TEST NAME: Alcohol Consumption Report

These 173 methylation marks are combined together in an algorithm the researchers named "DunedinPACE" for Dunedin (P)ace (o)f (A)ging in (m)ethylation. The average person has a DunedinPACE value of 1, which indicates a single year of biological aging per chronological year. Among Dunedin Study participants, the range of values extends from just above 0.6 (indicating an aging rate nearly 40 percent slower than the norm) to nearly 1.4 (indicating an aging rate 40 percent faster than the norm).

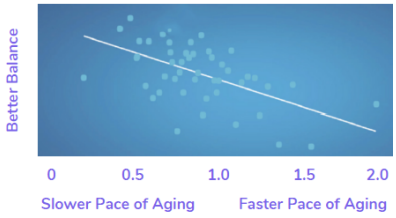
In order to validate the algorithm, the researchers used samples from participants in three other long-term studies. This analysis verified that the individuals whom the algorithm identified as aging faster; had a greater risk of poor health, developing chronic disease, or dying earlier. Similarly, those identified as aging more slowly performed better on tests of balance, strength, walking speed, and mental ability, and additionally, they appeared physically younger than trained raters for physical signs of aging.

Additionally, the DunedinPACE researchers used the test on participants in a randomized trial testing whether restricting calories had the potential to extend a healthy lifespan. The results suggested that the calorie restriction could counter the effects of an accelerated pace of aging.

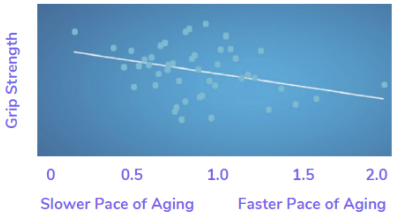
Thanks to this study's promising findings, the test developed by the Dunedin Study team will provide an alternate way of measuring whether age-slowing treatments work. This algorithm has the potential to allow faster testing of therapies able to extend the healthy lifespan of humans.

The following graphs are NOT your personal data. These graphs show how the increased rate of aging affects performance from the Dunedin cohort.

One-Leg Balance Test

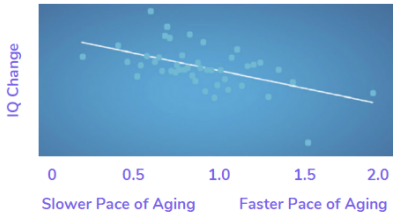


Grip Strength

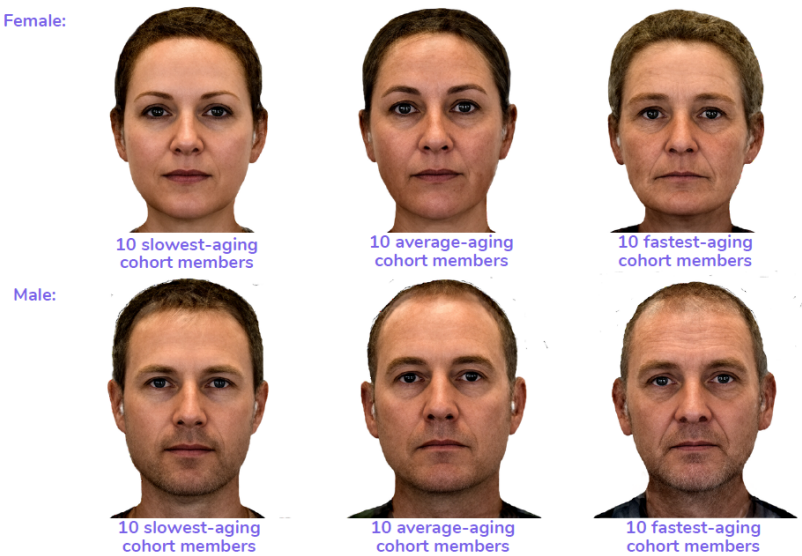


Cognitive Decline

(IQ Change from Childhood to Age 45)



Significant Variation in Facial Aging



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TEST NAME: Alcohol Consumption Report

UNDERSTANDING

The value and algorithm.

How Is This Algorithm Game-Changing?

This is a report about an individual's rate of aging. Most epigenetic tests take a snapshot of biological age at the moment in time when the test was taken, but because DunedinPACE determines the pace of aging, it is able to differentiate prior biological age factors and the rate of aging at that given time. The pace of aging in a methylation algorithm outperforms a number of other methylation-based biological clock algorithms because its data is unmatched, making DunedinPACE one of the best predictors of health outcomes.

The algorithm is noteworthy because it considers the details of one's life and by doing so it interprets your epigenetic alterations to determine the best reading of how you age. Other biological age clock outcomes are dampened by the influences across one's lifetime and will compound the negative outcomes instead of predicting how fast a person is aging at the time of testing. DunedinPACE can interpret small adjustments to your lifestyle while still taking into consideration methylation patterns from earlier years to produce a robust measurement of how one biologically ages.

The algorithm was developed from data collected from the Dunedin study group. The significance of this study was minimizing variables. The Dunedin cohort stands out by having its subjects all born within the same year. All current methylation clock algorithms have been developed to identify the methylation patterns that characterize individuals of different chronological ages. The limitation of these other algorithms is that the study group consists of individuals born in different years who also grew up in different historical conditions.

People the algorithm identified as having a faster pace of aging had a greater risk of poor health, chronic disease, and premature death. Other methylation-clock algorithms have been developed to identify methylation patterns that characterize individuals of different chronological ages which imposes a series of limitations on the outcomes being provided by. These other methylation-clock algorithms display their outcomes as an unwavering point instead of where your aging is currently.

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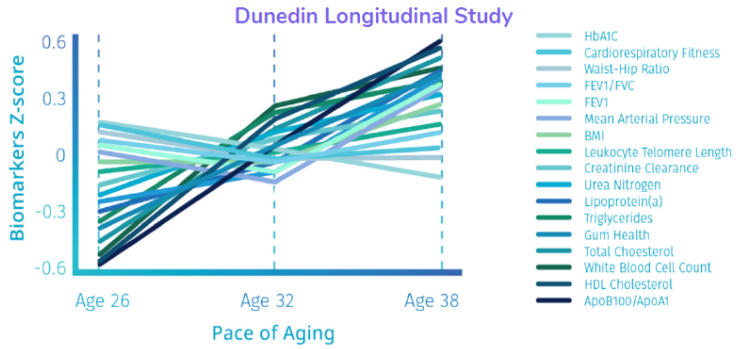
TEST NAME: Alcohol Consumption Report

How It Compares Against Other Methylation Clocks

Unlike any other biological test out there, the DunedinPACE Algorithm doesn't let us see your biological age, but instead, it looks at how fast you are aging. There are a number of benefits of knowing your pace of aging versus your age at a set point in time. By 2050, the world population aged 80 years old and above will more than triple, approaching more than 400 million individuals. This useful measure is non-invasive, inexpensive, reliable, and highly sensitive to biological change; making it an easy tool for health professionals to use to combat the challenges we will soon face with the growing aging population based on real-time measurements of interventions.

The Dunedin researchers tested if higher DunedinPACE levels, which indicate faster aging, were correlated with older chronological age. Mortality rates increase with advancing chronological age, although there may be some slowing at older ages. This suggests the hypothesis that the rate of aging increases across much of the adult lifespan. Consistent with this hypothesis, understanding society participants with older chronological age tended to have faster DunedinPACE value.



The above chart shows the Dunedin Longitudinal Study. Dunedin researchers collected a blood panel of 19 markers (shown above) and organ-system-function biomarkers at four successive waves of the Dunedin Study. By using repeated measures of data the study members were aged 26, 32, 38, and 45 years old.

They calculated the rate of change in each biomarker and how each individual's rate of change differed from the cohort's norm. Then they combined the individual's 18 personal rates of change across the panel of biomarkers to compute a composite for each study member, which is how they determine the pace of aging.

The Dunedin Study

The Dunedin cohort is one of the most remarkable resources for studying human biology. This is not the biggest nor the longest longitudinal study conducted, but it is special because it has a very high retention rate of participants. With 95% of the original cohort remaining in the study since its launch, the Dunedin cohort is the most closely examined group on earth. To put in perspective a good retention rate for longitudinal studies is between 60 to 80 percent of the original cohort population. [11]

Previous studies have attempted to measure the pace of aging by analyzing DNA methylation differences between people of different chronological ages. However, the "limitation of this approach is that individuals born in different years have grown up under different historical conditions, with a possibility of more exposure to childhood diseases, tobacco smoke, airborne lead, and less exposure to antibiotics and other medications, as well as lower quality nutrition -- all of which affect DNA methylation. An alternative approach is to study individuals who were all born the same year, and find methylation patterns that differentiate those who have been aging biologically faster or slower than their same-age peers." [3] The Dunedin study focuses on a one-year age cohort makes it more effective at tracking its participants, which contributes to the low number of extraneous variability in the results.

Following the one-year birth cohort, the repeated measures of data were collected via blood when the study members were 26, 32, 38, and 45 years old to quantify their rates of biological aging. The gathered data represents a personal rate of multi-organ system decline over a dozen years which determines the algorithm for pace of aging.

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EDUCATIONAL CONTENT

Report references.

About Us: The Dunedin Study - Dunedin Multidisciplinary Health & Development Research Unit. The Dunedin Study - DMHDRU. https://dunedinstudy.otago.ac.nz/about-us.

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PATIENT: XXXXXXXXXXXXXXX
TEST NUMBER: G-NL-XXXXXXX
GENDER: XX
AGE: XX

COLLECTED: 23-Mar-2023
RECEIVED: 01-Mar-2023
TESTED: 01-Mar-2023

TEST REF: GNL-NL-XXXXX
PRACTITIONER:
SSSSSSSSSSS
XXXXXXXXXXXXXXXXXXX

TEST NAME: Immune Report

TRUAGE BY TRUDIAGNOSTIC

Immune

This report explores the impacts of various types of immune cells and their concentrations on biological age by examining associated methylation patterns at various locations of your DNA.

Developed By TruDiagnostic's Bioinformatics & Research Department

UNDERSTANDING

Biological aging & the immune system.

Do you ever wonder why many older adults experience a harder time battling diseases like COVID-19 or the common flu, compared to younger people who typically have an **easier time recovering** from the same illnesses?

It all boils down to the capabilities of one's immune cells to effectively respond to internal and foreign health threats; capabilities which tend to decrease with age. **This age-related decline of the immune response in our blood is called immunosenescence**.

As we get older, and immunosenescence occurs, higher incidences of infections, cancer, and autoimmune disease emerge. As research indicates, the progression of one's immune system decline, to the point of immunosenescence, **occurs faster in men than in women**. It is also characterized by age-related changes in immune cells and inflammatory mediators.

Immunosenescence also **changes the number of immune cells** in our blood. The average adult has more than five liters of blood in their body that carries oxygen and nutrients to living cells and disposes of cellular waste. Blood also delivers various types of **immune cells, which are types of white blood cells** (WBC), to fight infections throughout the body. These WBCs come in many different shapes and sizes, and the concentration of each immune cell type has varying associations with age-related DNA methylation patterns.

JANE DOE | ID # ABC123
COLLECTED: 06/01/2020 | REPORTED: 07/01/2020

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THE REASON WHY

Immune cells are important to all epigenetic algorithms.

As we age, we have **overall fewer** Naïve T Cells, Natural Killer Cells, Macrophages, Dendritic Cells, and other immune cell types throughout our body. However, concentrations of immune cell types also change based on what kind of sample or tissue you are analyzing, such as blood or saliva, regardless of age.

Each immune cell type, and its respective concentration, can indicate vastly different aging implications from other types of immune cells when isolated; forcing algorithm developers to ask, *'Is this pattern actually caused by aging, or is this pattern caused by the type of cell and the type of tissue we are examining?'*

Further potential for data pollution rests in whether or not someone's immune system was actively or recently fighting an illness at the time of sample collection; which can cause temporary changes in immune cell concentrations.

Say we were to isolate Naïve CD8T immune cells from Memory CD8T immune cells (both of which are found in different concentrations in your blood sample) to determine your biological age based on those cells alone. **The Naïve CD8T cells might say you're 40 years old**, for example, **while the Memory CD8T cells would say you're 55 to 60 years old.**

Instead of addressing this challenge by completely excluding immune biomarkers, all of our algorithms were trained and developed with a weighted and controlled representation of each immune cell type and its concentration in blood tissue.

In doing so, we can ensure accurate results, free of potentially corrupting biodata. This includes our novel OMICm Age algorithm, as well as our other custom algorithms that have been developed to, as well as our other custom algorithms that have been developed to **ensure changes in immune cells don't give us false information about your biological age.**

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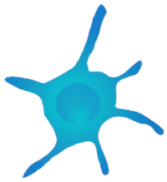
TEST NAME: Immune Report

THE IMPACTS OF

Immunosenescence on different immune cell types.

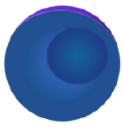
T Lymphocyte

- Reduced development and numbers of Naïve CD4T+/CB+ T cells
- Decline in CD4T+ function and in CD8T+ T cell totoxicity+ proliferation
- Reduced generation of Th subsets



Dendritic Cell

- Reduced IFN production and expression CD25 and ICAM-1 in mature MODCs
- Reduction in lymphocyte cytotoxicity and greater of monocyte-macrophage derived APCs



B Lymphocyte

- Reduced development and numbers of Naïve B cells
- Decreased diversity of B cell repertoires and B cells responses to new antigens

Macrophage

- Defective phagocytosis
- Decreased cytokine production, antigen presentation, and superoxide anion production

Neutrophils

- Decreased phagocytosis, chemotaxis, and apoptosis function

Natural Killer

- Reduced cytolytic potential and CD1 expression in NKT cells
- Decreased cytokine and chemokine production

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TEST NAME: Immune Report

Your Results.

IMMUNE CELL TYPE	95% CONFIDENCE INTERVAL RANGE	YOUR PERCENTAGE	MEAN	SD	# OF STANDARD DEVIATIONS ABOVE OR BELOW MEAN	IS THIS HIGHER OR LOWER THAN ANTICIPATED?
Naïve CD4T	7.196%-7.35%	3.59%	7.273	0.0383	1.446	HIGHER
Memory CD4T	5.14%-5.284%	2.05%	5.212	0.0361	1.647	HIGHER
Memory CD8T	6.519%-6.691%	9.00%	6.605	0.0430	1.346	HIGHER
Naïve CD8T	1.09%-1.16%	0%	1.125	0.0175	1.545	HIGHER
Basophils	1.026%-1.056%	0.77%	1.041	0.0076	2.389	HIGHER
B Memory	1.689%-1.785%	1.03%	1.737	0.0241	-1.57	LOWER
Naïve B	2.207%-2.311%	0%	2.259	0.0260	2.987	HIGHER
Regulatory T	0.604%-6.408%	2.89%	3.506	1.4510	-2.316	LOWER
Eosinophils	0.376%-0.424%	0%	0.400	0.0121	3.205	HIGHER
Natural Killer	3.353%-3.459%	5.08%	3.406	0.0264	-1.365	LOWER
Neutrophils	62.899%-62.953%	74.86%	62.93	0.0136	-1.781	LOWER
Monocyte	4.453%-4.567%	0.73%	4.510	0.0285	-2.981	LOWER

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XXXXXXXXXXXXXXXXXXX

TEST NAME: Immune Report

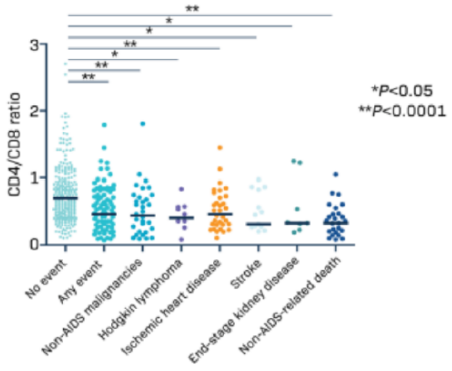
UNDERSTANDING

CD4T/CD8T Cell Ratio.

CD4T/CD8T cell ratio is incredibly informative on disease. A value between 1 and 4 is ideal. A value between 0 and 1 marks an "inverted ratio". A low or inverted CD4T/CD8T ratio is an immune risk phenotype and is **associated with altered immune function, immune senescence, and chronic inflammation**.

The prevalence of an inverted CD4T/CD8T ratio increases with age. An inverted ratio is seen in 8% of 20-59 year olds and in 16% of 60-94 year olds. Women across all age groups are less likely to have an inverted ratio than their male counterparts.

Age and hormone-related atrophy of the thymus are theorized to explain the differences between populations. Hormonal influence on the ratio is supported by a correlation between low Plasma Estradiol levels, high circulating CD8T, and low CD4T/CD8T ratios in women with premature ovarian failure.



We have been able to refer patients for additional testing to diagnose HIV, Chronic Lymphocytic Leukemia, and even individuals taking their Rapamycin at too high of a dose. **If you see a low CD4T/CD8T ratio, it is not an immediate cause for concern but we might recommend testing via traditional labs just in case**. A value of 4+ marks hyperactivity or possible infection, autoimmunity, or additional immune risk phenotypes.

CELL TYPE	REFERENCE RANGE	YOUR RATIO	MEAN	SD	# OF STANDARD DEVIATIONS ABOVE OR BELOW MEAN	IS THIS HIGHER OR LOWER THAN ANTICIPATED?
CD4T/CD8T T Cell Ratio	1.00-4.00	1.61	2.59	0.074	1.469	HIGHER

RATIO	ABOUT THIS RATIO	YOUR VALUE
Regulatory T Cells to Total T Lymphocytes (RegT/all other T Cells)	There is evidence that Tregs exhibit atheroprotective properties by suppression of autoreactive T cell responses or by secretion of anti-inflammatory cytokines (Pastrana et al., 2012). Thus this might be a marker for cardiovascular disease. (www.sciencedirect.com)	0.147
Adaptive to Innate Immune (A/A Ratio)	The adaptive-to-innate immune ratio (A/I ratio) has been linked to response to several types of immunotherapy.	0.517

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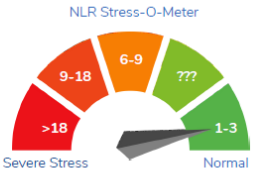
TEST NAME: Immune Report

Other Ratios to Prioritize.

RATIO	ABOUT THIS RATIO	NORMATIVE RATIO	YOUR VALUE
Neutrophil to Lymphocyte	The NLR is simply the number of Neutrophils divided by the number of Lymphocytes. Under physiologic stress, the number of Neutrophils increases, while the number of Lymphocytes decreases. The NLR ***combines*** both of these changes, making it more sensitive than either alone: Effect of Physiologic Stress on the NLR: ↑↑ NLR= Neutrophils / Lymphocytes Endogenous cortisol and catecholamines may be major drivers of the NLR. Increased levels of cortisol are known to increase the neutrophil count while simultaneously decreasing the lymphocyte count. Thus, NLR is not solely an indication of infection or inflammation. Any cause of physiologic stress may increase the NLR (e.g. hypovolemic shock).	 Neutrophil-to-Lymphocyte ratio (NLR) reflects the amount of physiologic stress. The optimal cutoff value will vary depending on the specific patient population and disease state. The numbers provided above are. intended merely to provide a general concept of NLR interpretation.	1.724
Monocyte to Lymphocyte	MLR (Monocyte to Lymphocyte ratio) has been demonstrated to be a novel hematological and inflammatory parameter. MLR is associated with various diseases, such as community-acquired pneumonia, axial spondylarthritis, and coronary angiography, as well as the systemic inflammatory response, which reflects the abnormal immune status of diseases.	The mean Neutrophil-to-Lymphocyte ratio in the whole population was 1.70±0.70 (Range: 8.38, Min: 0.23, Max: 8.61), mean lymphocyte-to-monocyte ratio was 11.15±3.14 (Range:23.21, Min:3.46, Max:26.67), and mean platelet-to-lymphocyte ratio was 117.05±47.73 (Range:93.60, Min:19.11, Max:1598.77).	11.45

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TEST NAME: Immune Report

THE PERCENTAGE OF

Immune cells in our blood can be highly informative to health.

'Health outcomes' is a term used to encompass an interconnected set of attributes, that cumulatively describe the consequences of disease for an individual; aka, **how extensively does an illness impact your life and overall health**?

These attributes include impairments, symptoms, functioning capabilities, participation in activities and social roles, and overall health-related quality of life. Health outcomes also tell us how long, on average, people live within a given community, and how much physical and mental health they experience within their lifetime.

There are **many factors that impact health**, such as education, environment, lifestyle habits, access to healthcare, and socioeconomic stability.

There are also **many immune cell types** that are influenced by these factors, and that have direct associations with health risks and outcomes. Some of these include **Naïve CD4T** and **Naïve B** T-cells, which help protect the body from infection and cancer, **Natural Killer** immune cells that use enzymes to kill infected and cancerous cells, as well as **Memory CD4T** and **Memory B** T-cells which help the immune system coordinate and adapt its response.

Naïve CD4T

Decreased concentrations have been associated with an increased risk of COPD and Type 2 Diabetes, but decreased risk of all-cause mortality.

Naïve B

Decreased concentrations have been associated with a decreased risk of all-cause mortality.

Memory CD4T

Decreased concentrations have been associated with an increased risk of all-cause mortality.

Memory B

Increased concentrations have been associated with an increased risk of cancer, but decreased risk of Type 2 Diabetes.

Natural Killer

Decreased concentrations have been associated with a decreased risk of all-cause mortality.

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TEST NAME: Immune Report

Immune cells impact health outcomes regardless of age, sex, race, smoking habits, obesity, and alcohol consumption. However, **lifestyle habits and environmental factors can impact the quantity of, and health of, different immune cells**. For example, research shows a decrease in Natural Killer cell counts associated with smoking, obesity, and stress levels.

DNA methylation patterns show that certain lifestyle and environmental factors are **associated with increases and decreases in specific types of immune cells**. As the concentration of these cells changes, so does the risk for diseases such as stroke, Type 2 Diabetes, COPD, depression, cancer, and more.

	AGE	BMI	ALCOHOL	EXERCISE
ASSOCIATED WITH higher levels of	Memory CD4T B Memory Natural Killer (NK) Neutrophils Monocyte	Memory CD4T	Memory CD4T Basophils Monocyte	Natural Killer (NK) Monocyte
ASSOCIATED WITH lower levels of	Naïve CD4T Naïve CD8T Regulatory	Naïve CD4T Naïve CD8T Regulatory Natural Killer (NK)		Naïve B

SLEEP	SMOKING	CAFFEINE	STRESS	MATERNAL SMOKING
▲ Natural Killer (NK)	▼ Natural Killer (NK)	▲ Naïve CD4T	▼ Natural Killer (NK)	▼ Memory CD8T

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TEST REF: GNL-NL-XXXXX
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XXXXXXXXXXXXXXXXXXX

TEST NAME: Immune Report

CELL TYPE	FACTOR WHICH ARE ASSOCIATED WITH HIGHER LEVELS	FACTORS WHICH ARE ASSOCIATED WITH LOWER LEVELS
Naïve CD4T	Alcohol, Caffeine	Age, BMI
Memory CD4T	Alcohol, Age, BMI	
Memory CD8T		Maternal Smoking
Naïve CD8T		Age, BMI
Basophils	Alcohol	
B Memory	Age	
Naïve B		Exercise
Regulatory		Age, BMI
Eosinophils		
Natural Killer	Sleep, Exercise, Age	Stress, BMI, Smoking
Neutrophils	Age	
Monocyte	Age, Alcohol, Exercise	

Notably, Naïve CD4T+ T-cell, Naïve B-cell, and Natural Killer cell fractions are all associated with a reduced risk of all-cause mortality, even after adjustment for all major disease risk factors. Interestingly, whilst the Naïve CD4T+ T-cell fraction also displayed negative associations with many health outcomes, notably with COPD and Type 2 Diabetes (T2D), the Memory CD4T+ T-cell fraction was only negatively associated with all-cause mortality. An increased Memory B-cell fraction was specifically associated with an increased risk of cancer but a reduced risk for T2D, whilst no associations were observed for the other outcomes.

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A SCIENTIFIC DEEP DIVE

Methods & Applications

You may be wondering how it's possible that every cell in your body has the same DNA, but a heart cell behaves like a heart cell, and a hair cell behaves like a hair cell, etc. The answer is epigenetics! Epigenetics controls cell development and function by **switching certain genes on and off, which determines phenotype and how your cells behave**. It makes sense that the epigenetic regulation of each cell would depend on its cell type. You wouldn't want your heart to make the proteins found in your hair and vice versa. Thus, each cell has a different **epigenetic signature**.

This means that in order to create an accurate, predictive algorithm from DNA methylation data, one must know **what cell types** are being tested. Otherwise, the information from these **algorithms can give false information**.

For example, if you were to test your brain cells, you would see lower biological ages than if testing blood. We also see that breast tissue can age faster than other tissues across the rest of our body. The same is true with blood if someone is sick and they have increased B cells (cells that produce antibodies), that could alter results in a way that is not consistent with the actual health of an individual.

Therefore, the **rate of aging we calculate is dependent on what cell types we measure**. Using blood as the sample type, we determine what cells are we looking at, and more importantly, we control for different cell representations so our algorithm is accurate and predictive.

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TEST NAME: Immune Report

Immune Deconvolution.

As cells differentiate from pluripotent stem cells to the tissue type they become, they start to **form unique DNA methylation** patterns that can tell us which cell type they belong to.

By analyzing DNA methylation patterns in a tissue sample, we can infer the relative abundance of different cell types present in that sample. This is because different cell types have distinct DNA methylation profiles. With that information, we create algorithms that use DNA methylation to estimate the relative proportions of different cell types within a tissue sample.

Overall, this technique allows TruDiagnostic to gain a **better understanding of the cellular composition of a complex tissue sample**, which can be useful for understanding disease processes and monitoring the effects of interventions.

Accuracy of Results.

We've successfully demonstrated that our testing is comparable with the gold standard of Flow Cytometry with **less than 3% error**. We believe this is a needed algorithm to improve all methylation analysis algorithms in the future, and we have also developed a saliva deconvolution method for this very reason.

This immune deconvolution tool has been used in large biobank datasets to look at associations and trends. We believe that this might be a great tool to quantify the immune system and to find novel associations to disease conditions without having to use Flow Cytometry; which can be expensive, require high volumes of blood, and requires refrigerated sample processing.

Research & Partnerships.

The algorithms we've used to generate your results in this report are a product of academic processing and analysis from our private epigenetic database, along with research partnerships with Harvard University, Johns Hopkins University, and the Chinese Academy of Sciences.

Additionally, research into senescence has grown exponentially over the last few years. However, there are still very few tools to easily quantify this process. With Ohio State, we have created senescence predictors of t-cells through DNA methylation.

We are **now developing methods** to apply this to all tissues with additional datasets and believe this will be a valuable tool to quantify this hallmark of aging.

A meta-analysis of immune cell fractions at high resolution reveals novel associations with common phenotypes and health outcomes

Qi Luo, Varun B. Dwaraka, Qingwen Chen, Huige Tong, Tianyu Zhu, Kirsten Seale, Joseph M Raffaele, Shijie C. Zheng, Tavis L. Mendez, Yulu Chen, Sofina Begum, Kevin Mendez, Sarah Voisin, Nir Eynon, Jessica A. Lasky-Su, Ryan Smith, Andrew E. Teschendorff

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PATIENT: XXXXXXXXXXXXXXX			TEST REF: GNL-NL-XXXXX
TEST NUMBER: G-NL-XXXXXXX	COLLECTED: 23-Mar-2023		PRACTITIONER: SSSSSSSSSSS
GENDER: XX	RECEIVED: 01-Mar-2023		
AGE: XX	TESTED: 01-Mar-2023		XXXXXXXXXXXXXXXXXXX

TEST NAME: Telomere Length Report

TRUAGE BY TRUDIAGNOSTIC

Telomere Length

This report explores telomere length and its relation to biological age and accelerated biological aging by examining associated methylation patterns at various locations of your DNA.

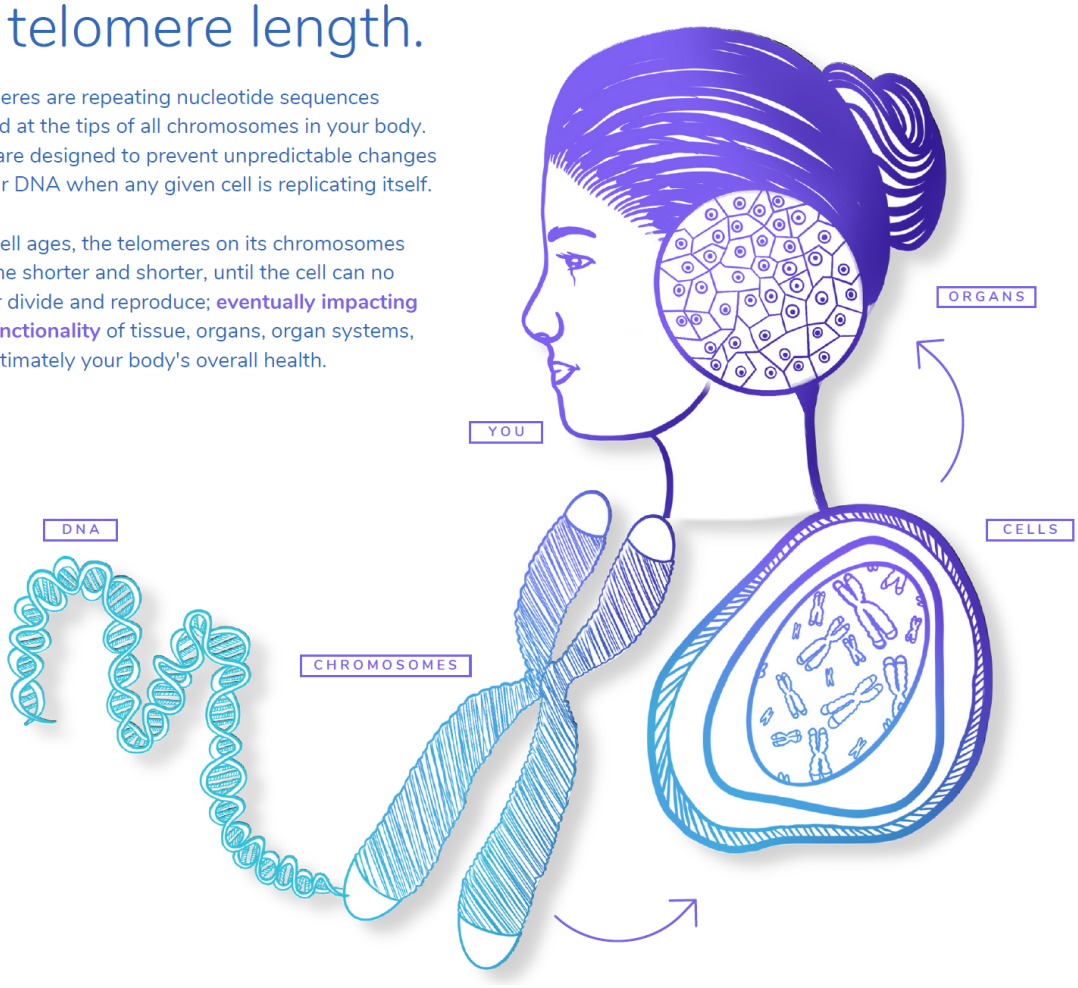
Developed By TruDiagnostic's Bioinformatics & Research Department

UNDERSTANDING

The importance of telomere length.

Telomeres are repeating nucleotide sequences located at the tips of all chromosomes in your body. They are designed to prevent unpredictable changes to your DNA when any given cell is replicating itself.

As a cell ages, the telomeres on its chromosomes become shorter and shorter, until the cell can no longer divide and reproduce; **eventually impacting the functionality** of tissue, organs, organ systems, and ultimately your body's overall health.



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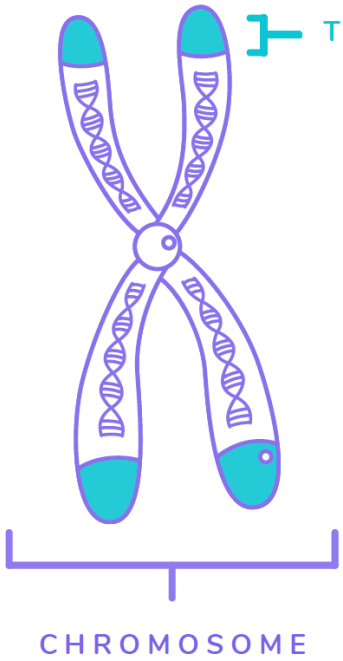
TEST NAME: Telomere Length Report



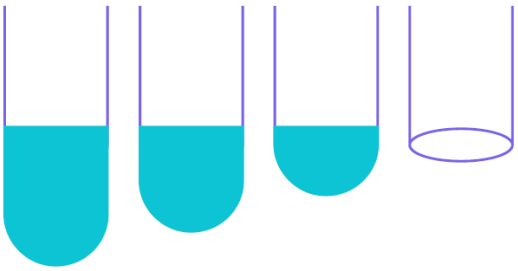
A telomere's primary function is to prevent chromosomal “fraying” when a cell replicates, much like the plastic tips on the end of shoelaces [5]. As a cell ages, its telomeres become shorter.

This shortening is thought to be one of several factors that causes cells to age. In actively dividing cells, such as those in the bone marrow, the stem cells of the embryo, and germ cells in the adult, telomere length (TL) is kept constant by the enzyme telomerase.

As humans age, this enzyme becomes less active over time. This leads to a slow decrease in telomere length, **until a point is reached at which the cell is no longer capable of replication** (replicative senescence).

A cell can no longer divide when telomeres are too short—once they reach a critical point, the cell becomes inactive (or senescent), slowly accumulating damage that it can’t repair, or it dies [6].

Telomere length is **affected by both genetic and epigenetic contributions**. A new study found that DNA methylation is closely linked to TL. The study by researchers at the University of California Los Angeles shows a very significant linkage between two different markers that indicate aging [2].



AS CELLS DIVIDE OVER TIME, TELOMERES SHORTEN UNTIL CELL DIVISION STOPS.

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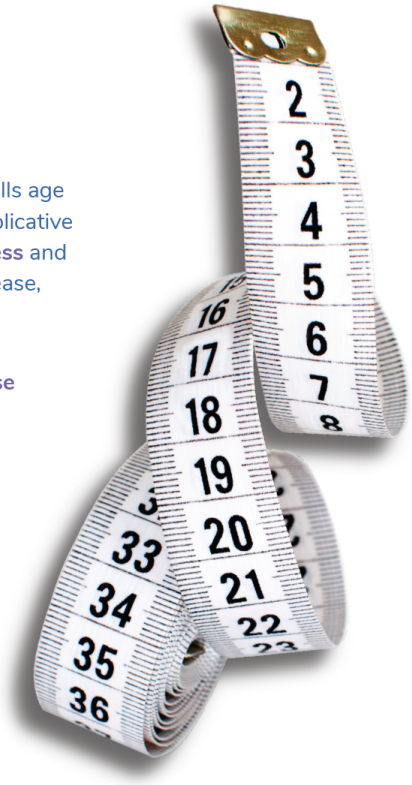
TEST NAME: Telomere Length Report

WHY TELOMERE

Length is important.

Telomeres are an essential part of human cells that affect how our cells age [1]. Telomere length has emerged as an important determinant of replicative senescence and cell fate - **an important indicator of the aging process** and a wide range of disease states, including cancers, cardiovascular disease, and age-related disorders.



Shorter telomeres are not only associated with age but with disease too. In fact, shorter telomere length and low telomerase activity are associated with several chronic preventable diseases. These include hypertension, cardiovascular disease, insulin resistance, type 2 diabetes, depression, osteoporosis, and obesity.

Shorter telomeres have also been implicated in genomic instability and oncogenesis. **Older people with shorter telomeres have three and eight times increased risk to die from heart and infectious diseases**, respectively [4]. The rate of telomere shortening and telomere length is therefore critical to an individual's health and pace of aging.

JANE,

at your chronological age of 61, your telomeres are

LONGER THAN 90%

of people who share the same chronological age as you.

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PATIENT: XXXXXXXXXXXXXXX
TEST NUMBER: G-NL-XXXXXXX
GENDER: XX
AGE: XX

COLLECTED: 23-Mar-2023
RECEIVED: 01-Mar-2023
TESTED: 01-Mar-2023

TEST REF: GNL-NL-XXXXX
PRACTITIONER:
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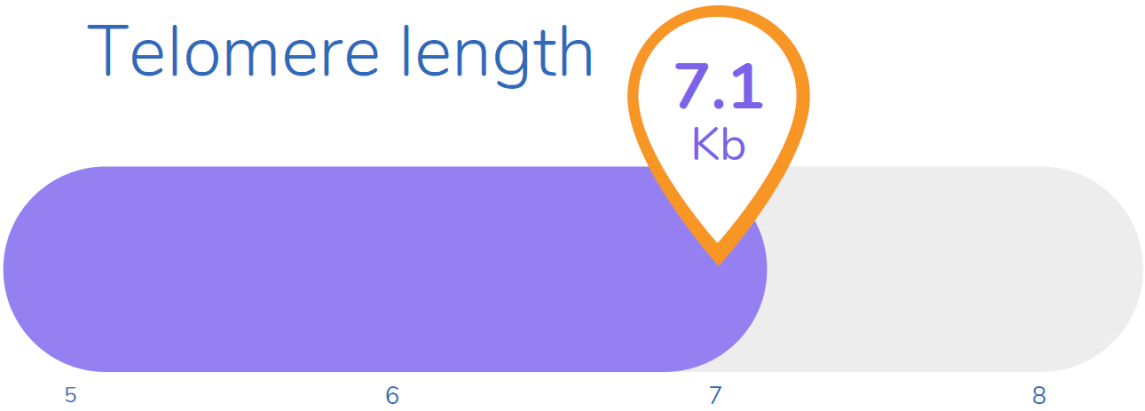
TEST NAME: Telomere Length Report

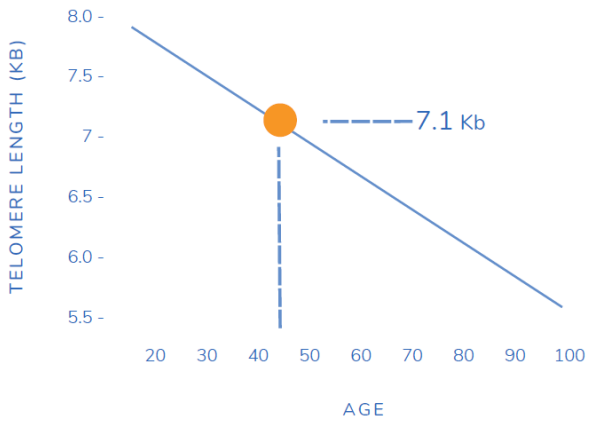
YOUR AVERAGE

Telomere length



If we were to estimate your biological age **strictly from your telomere measurement**, we would anticipate your age to be:

At your chronological age of 50, you would be in the **90th** percentile of telomere length compared to others of your same chronological age.



This means that your telomeres are longer than **90**% of people who share the same chronological age as you. Simply put, longer telomeres equal healthier telomeres and cells.

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EDUCATIONAL CONTENT

FAQs

TOP QUESTIONS

Can Telomere length be increased with therapies or behaviors?

It is important to note that the research in this field is still evolving, and the effects of different interventions on telomere length are not yet fully understood.

1. Lifestyle and Behavioral Factors:
Telomeres are the protective caps at the ends of chromosomes that shorten with each cell division. Telomere length has been associated with aging and various age-related diseases. While telomere shortening is a natural part of the aging process, there has been considerable interest in finding ways to potentially increase telomere length through therapies or behaviors.

It is important to note that the research in this field is still evolving, and the effects of different interventions on telomere length are not yet fully understood. As a result, no definitive method to elongate telomeres current exists in somatic cells. However, there is some information which alludes to helpful intervention.

Several studies have explored the relationship between lifestyle factors and telomere length. While no definitive causative links have been established, certain behaviors have been associated with longer telomeres:

a. Physical Exercise: Regular physical exercise has been linked to longer telomeres. A study by Ludlow et al. (2008) found that individuals who engaged in moderate or vigorous physical activity had longer telomeres compared to those who were sedentary.

b. Diet: Some research suggests that a healthy diet, rich in fruits, vegetables, whole grains, and lean proteins, may be associated with longer telomeres. Conversely, diets high in refined sugars and unhealthy fats may be linked to shorter telomeres. However, more research is needed to establish definitive conclusions in this area.

c. Stress Reduction: Chronic psychological stress has been associated with telomere shortening. Stress reduction techniques such as mindfulness meditation and stress management programs may have potential benefits for telomere maintenance. One study by Epel et al. (2004) showed that caregivers of chronically ill children who practiced mindfulness meditation had increased telomerase activity, an enzyme that helps maintain telomere length.

2. Pharmacological Interventions:
Several studies have explored the potential of pharmacological interventions to influence telomere length. It is important to note that these interventions are still at an experimental stage and require further research before being established as effective or safe for widespread use. Here are a few examples:

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a. Telomerase Activators: Telomerase is an enzyme that can elongate telomeres. Certain compounds, such as small-molecule telomerase activators, have been investigated for their potential to increase telomerase activity and lengthen telomeres. One such compound is TA-65, which has shown promising results in preclinical studies and early human trials. However, more research is needed to determine its mechanism.

b. Lifestyle Modification + Pharmacological Intervention: A study by Ornish et al. (2013) investigated the effects of comprehensive lifestyle changes, including a plant-based diet, exercise, stress reduction, and social support, in combination with a telomerase activator. The intervention group showed significant increases in telomere length over a five-year period compared to the control group.

It is essential to consult with medical professionals and researchers for the most up-to-date information regarding telomere lengthening therapies, as the field is continually advancing and new research may have emerged since this report has been created.

What factors have been shown to modify epigenetic predictors of telomere length?

In the original DNAm Telomere length algorithm created by Dr. Steve Horvath from UCLA, they saw several associations between lifestyle factors and DNAm Telomere length. They found omega-3 supplement intake was correlated to longer age-adjusted DNAmTL. The effect of omega-3 supplementation was more pronounced in males than in females. In fact, omega-3 intake is associated with longer DNAmTLadjAge even after adjusting for sex, BMI, educational levels, and smoking pack year. In addition, this study showed that smoking was associated with shorter telomere lengths. Other studies have shown that traumatic stress and PTSD also show an association between telomere length and epigenetic clocks.

How much does telomere length compare to Epigenetic aging clocks?

Both epigenetic aging clocks and telomere length are used to measure aging. However, they approach this by measuring different hallmarks of aging. DNA methylation-based clocks generally tend to be superior at capturing aging. We know this because of their ability to predict negative outcomes associated with aging. Although telomere length has been a long-used biomarker of aging, they tend to not be very predictive. This is summarized well in a 2017 review paper on biological aging where the authors said, “Briefly, telomere length is extensively validated but has low predictive power.”

This is backed up by other analyses from the generation Scotland cohort. Evidence that TL and epigenetic clock estimates are independent predictors of chronological age and mortality risk was obtained in the study by Marioni et al. (2018) performed in two Scottish cohorts aged from 70 to 90 years. In both cohorts studied, combined whole-blood TL and DNAm age explained more variance in age than each of them individually. In combined cohort analysis, TL and DNAm age explained 2.8 and 28.5% of the variance in age, respectively, and jointly they explained 29.5%. This large difference was present using even only 1st generation chronologically trained clocks which are not as effective in predicting risk as the 2nd and 3rd generation clocks available today.

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TEST NAME: Telomere Length Report

How does DNAm Telomere relate to regular telomere length measures?

Leukocyte DNAmTL outperforms regular LTL (done via qPCR) in predicting

- Time-to-death
- Time-to-coronary heart disease
- Time-to-congestive heart failure
- Association with smoking history

It also has double the correlation to age than traditional telomere length.

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EDUCATIONAL CONTENT

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TEST NAME: Telomere Length Report

Boks MP, van Mierlo HC, Rutten BP, Radstake TR, De Witte L, Geuze E, Horvath S, Schalkwyk LC, Vinkers CH, Broen JC, Vermetten E. Longitudinal changes of telomere length and epigenetic age related to traumatic stress and post-traumatic stress disorder. Psychoneuroendocrinology. 2015 Jan;51:506-12. doi: 10.1016/j.psyneuen.2014.07.011. Epub 2014 Jul 23. PMID: 25129579.

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PATIENT: XXXXXXXXXXXXXXX			TEST REF: GNL-NL-XXXXX
TEST NUMBER: G-NL-XXXXXXX	COLLECTED: 23-Mar-2023		PRACTITIONER: SSSSSSSSSSS
GENDER: XX	RECEIVED: 01-Mar-2023		
AGE: XX	TESTED: 01-Mar-2023		XXXXXXXXXXXXXXXXXXX

TEST NAME: Type 2 Diabetes Risk Report

BEN'S TRIGLYCERIDES AND DIABETES RISK METHYLATION REPORT

ABCG1 (cg06500161), PHOSPHO1 (cg02650017), SOCS3, SREBF1, and TXNIP Genes

TruDiagnostic™

Are You At Increased Risk For Developing Type 2 Diabetes?

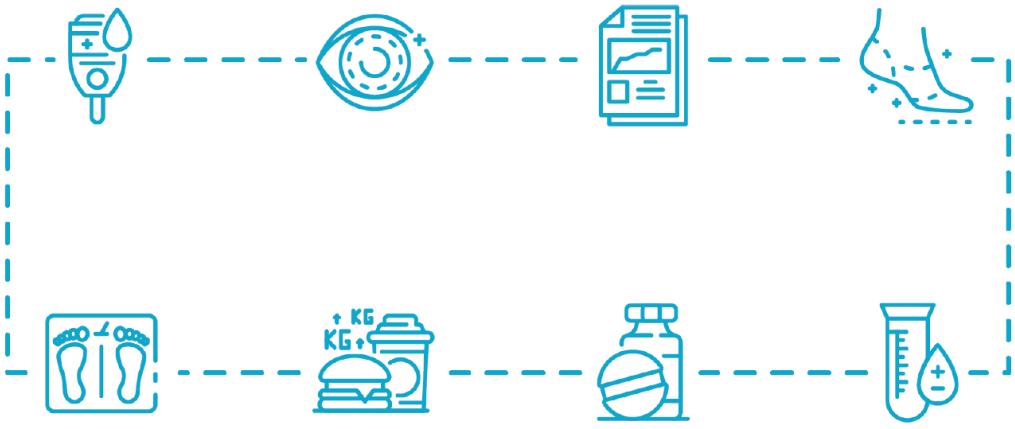
Epigenetic biomarkers for Type 2 Diabetes

Type 2 diabetes (T2D) is a complex disease that results from genetic and environmental interactions that can be modified and/or mediated by epigenetic changes. A number of genetic and non-genetic factors have been identified that increase the risk of T2D. However, a healthier lifestyle, including proper diet and exercise, can potentially reduce the risk of T2D by almost 50 percent in high-risk groups [3].

Therefore, there is great interest and need to identify individuals that have a high risk of developing T2D. By postponing and/or preventing T2D and its complications, it may be possible to reduce T2D-associated mortality and the financial cost of treating the disease and its complications.

To date, more than 65 genetic variants have been identified that increase the risk of T2D by almost 10 percent [8]. However, genetic screening for T2D risk variants has not been implemented in clinics. Despite the potential value of such screening tests, a number of limitations have hindered their use. These limitations include small effect size, their low discriminative ability, a small added value compared with the clinical risk factors, and a lack of models that take into account gene-gene and gene-environment interactions [3]. Failure to understand the pathophysiology of T2D hinders the efforts to develop improved therapeutic strategies [7].

There is great interest in epigenetic biomarkers such as DNA methylation, which, unlike the DNA sequence, can be influenced by the environment, and has the potential to improve T2D prediction [3]. Recently, an epigenome-wide association study identified 5 DNA methylation loci ***(ABCG1, PHOSPHO1, SOCS3, SREBF1, and TXNIP)*** in the blood that were associated with T2D. Furthermore, the study showed that a methylation score that combined the results from these 5 methylation loci found an association with prospective T2D occurrence [1].



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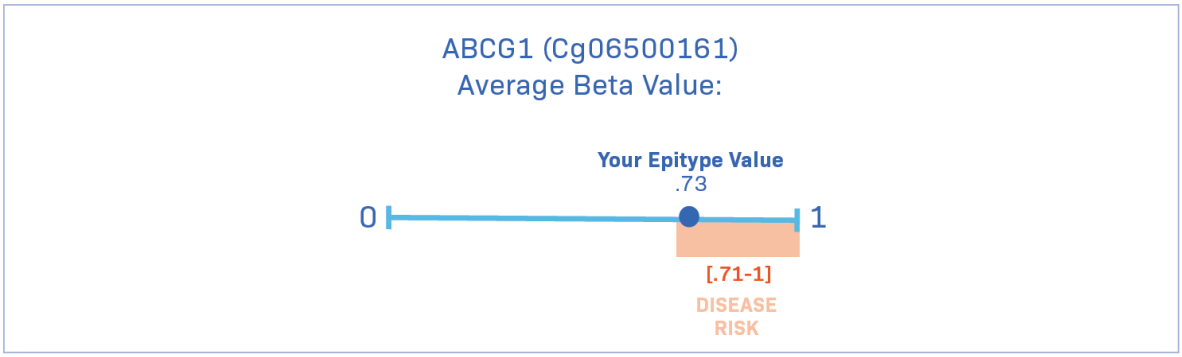
TEST NAME: Type 2 Diabetes Risk Report

What is ABCG1?

ABCG1 is a gene that encodes a member of the ATP-binding cassette (ABC) protein family, which plays a role in the homeostasis of glucose and lipids. These proteins do so by removing excess cholesterol from peripheral tissues and transporting it to the liver. The HDL-mediated increase in insulin secretion is dependent on ABCG1 [2]. Loss of both the ABCA1 and ABCG1 genes results in sterol accumulation, impaired glucose-stimulated insulin secretion, and inflammation of pancreatic ß-cells which can all lead to diabetes [6].

The ABCG1 marker has been replicated across different tissues in more than 10,000 individuals representing different ethnicities. Altered DNA methylation in ABCG1 is associated with the downregulation of mRNA levels from T2D individuals [2]. DNA methylation at this site in blood DNA has demonstrated to be functionally correlated with a number of T2D risk factors, such as BMI, triglycerides, and HbA1c [3].

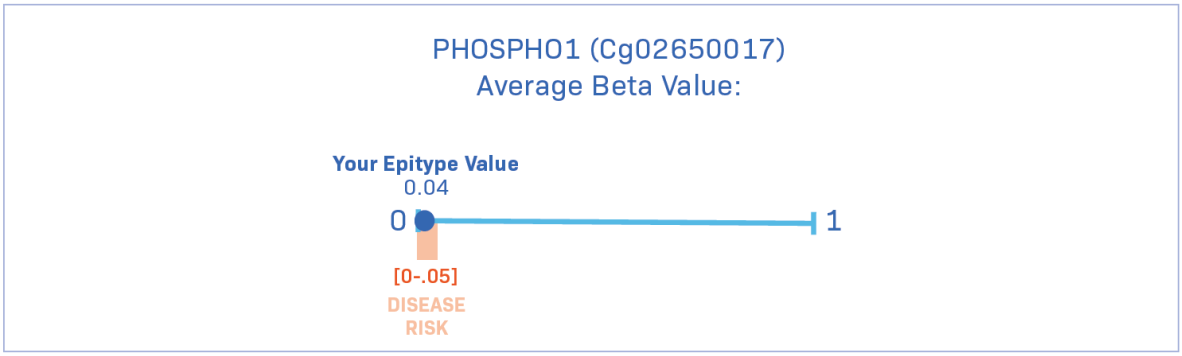
Your DNA methylation score at ABCG1 locus cg06500161 gives an indication of your level of risk for type 2 diabetes; if your score is 70.1% or greater it is associated with a 9% increased risk for future type 2 diabetes occurrence.



What is PHOSPHO1?

PHOSPHO1 encodes a phosphatase that is highly expressed in skeletal muscle and plays a role in skeletal mineralization. Under certain circumstances, it may also cause vascular mineralization. Cardiovascular calcification is a common consequence of aging, diabetes, and hypercholesterolemia. PHOSPHO1, is also considered to be an attractive target for cardiovascular therapy. Interestingly, it has been found that DNA methylation at the PHOSPHO1 locus cg02650017 in blood correlated positively with HDL levels. DNA methylation at the PHOSPHO1 locus cg02650017 is associated with future T2D risk [3].

A DNA methylation score of 5.0% or greater at the PHOSPHO1 locus cg02650017 in blood DNA was associated with a 15% decreased risk for future type 2 diabetes occurrence.



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TEST NAME: Type 2 Diabetes Risk Report

The Science

DNA methylation at the ABCG1 locus cg06500161 in blood DNA was associated with a 9% increased risk for future T2D (OR = 1.09, 95% CI = 1.02–1.16, P-value = 0.007, Q-value = 0.018), while DNA methylation at the PHOSPHO1 locus cg02650017 in blood DNA was associated with a decreased risk for future T2D (OR = 0.85, 95% CI = 0.75–0.95, P-value = 0.006, Q-value = 0.018) after adjustment for age, gender, fasting glucose, and family relation.

Furthermore, the level of DNA methylation at the ABCG1 locus cg06500161 in blood DNA correlated positively with BMI, HbA1c, fasting insulin, and triglyceride levels, and was increased in adipose tissue and blood from the diabetic twin among monozygotic twin pairs discordant for T2D. DNA methylation at the PHOSPHO1 locus cg02650017 in blood correlated positively with HDL levels [3].

THE IMPACT TO YOU

The impact to you is based on your level of methylation at these gene loci compared with the risk categories determined and assessed in the cited papers in regards to T2D risk.

Your DNA methylation score was _A__ at the ABCG1 locus and __B_ at the PHOSPHO1 locus.

Your DNA methylation scores at these gene loci would reflect __C__ according to the referenced study. [3]

Some studies on this particular CpG loci have suggested that fasting and low carb diets can reduce methylation at these loci to lower your risk. Please consult your doctor to discuss this and more treatment options.

Summary

Type 2 diabetes can be modified and/or mediated by epigenetic changes, and a number of genetic and non-genetic factors have been identified that increase the risk of T2D. Recent studies have found 5 DNA methylation loci associated with T2D occurrence. ABCG1 is a gene that insulin secretion is dependent on. Altered DNA methylation in ABCG1 is associated with the locus downregulation of mRNA levels from T2D individuals. DNA methylation at the ABCG1 locus cg06500161 in blood DNA was associated with an increased risk for future T2D and DNA methylation at the PHOSPHO1 locus cg02650017 in blood DNA was associated with a decreased risk for future T2D. DNA methylation at these loci is associated with cholesterol levels, triglyceride levels, ischemic stroke, and risk of T2D. Identifying T2D risk factors is fundamental for the prevention of

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TRUAGE BY TRUDIAGNOSTIC

Inflammation

This report explores the impacts of inflammation on biological age and accelerated biological aging by examining associated methylation patterns at various locations of your DNA.

Developed By TruDiagnostic's Bioinformatics & Research Department

UNDERSTANDING

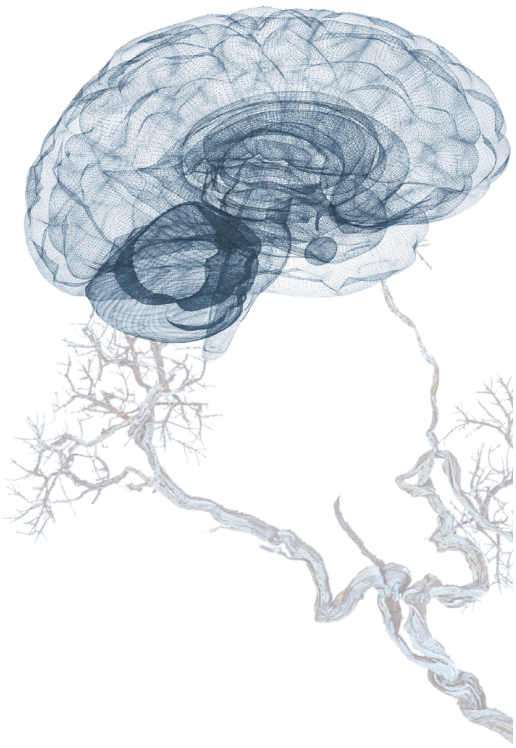
Inflammation's impact on cognitive health.

As we age, baseline levels of inflammatory biomarkers increase, leading to a decline in cognition. The cognitive processes that are negatively impacted by inflammation and age-related advanced inflammation can include things like memory, speed of processing, and overall **cognitive function**. Additionally, inflammation has been linked to the beginning stages of **dementia and neurodegenerative diseases**.

When aging occurs, epigenetic changes occur that promote inflammation. This causes a decrease in the global genome methylation, which then causes an increase in methylation to specific regions (including a notable impact on CD8+ and CD4+ T cells). Additionally, several studies indicate that DNA methylation is better associated with chronic inflammation than traditional measures; highlighting how epigenetic mechanisms play a major role in inflammatory imbalance. These mechanisms have also been linked to an **accumulation of cellular damage that can induce a constant inflammatory response**.

Acute inflammation is a biological response to harmful stimuli. However, chronic and elevated levels of inflammation can mark the development of **age-related diseases such as cancer, atherosclerosis, and Alzheimer's**. *Inflammaging, defined as an age-related increase in the levels of pro-inflammatory markers in blood and tissues, is a strong risk factor for multiple diseases that are highly prevalent and frequent causes of disability in elderly individuals.*

Through DNA methylation (DNAm) we have the ability to estimate the total extent of inflammation in your body. This is able to provide more in-depth insights into inflammation-related health information than traditional, inflammation-based bio-measurements can.



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PATIENT: XXXXXXXXXXXXXXX
TEST NUMBER: G-NL-XXXXXXX
GENDER: XX
AGE: XX

COLLECTED: 23-Mar-2023
RECEIVED: 01-Mar-2023
TESTED: 01-Mar-2023

TEST REF: GNL-NL-XXXXX
PRACTITIONER:
SSSSSSSSSSS
XXXXXXXXXXXXXXXXXXX

TEST NAME: Inflammation Report

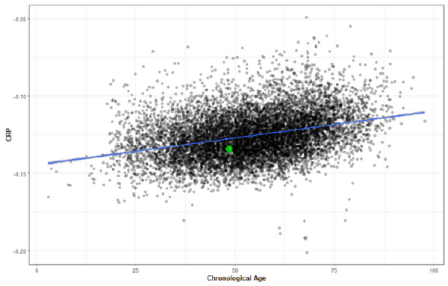
Your Results.

DISCLAIMER: All population graphs included in this report are based off of data from thousands of research participants and TruAge test takers.

Your **DNAm CRP** level is higher than

45%

of the population at your same calendar age and sex.



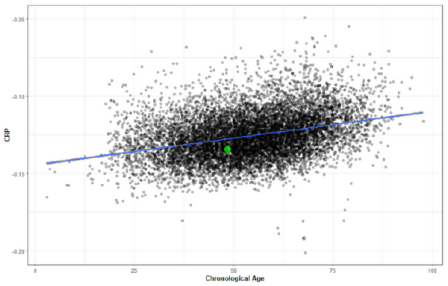
RESULTS OVER TIME

DNAm CRP is produced by the liver in response to acute inflammation. DNAm CRP has an inverse relationship with cognitive functions such as memory, speed, and visuospatial functions.

Your **DNAm IL-6** level is higher than

48%

of the population at your same calendar age and sex.



RESULTS OVER TIME

DNAm IL-6 is a widely used marker of inflammation, and circulating levels of the cytokine typically rise in older age. DNAm IL-6 is positively associated with BMI, self-reported smoking status, and alcohol intake.

JANE DOE | ID # ABC123
COLLECTED: 06/01/2020 | REPORTED: 07/01/2020

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GENDER: XX	RECEIVED: 01-Mar-2023		
AGE: XX	TESTED: 01-Mar-2023		XXXXXXXXXXXXXXXXXXX

TEST NAME: Inflammation Report

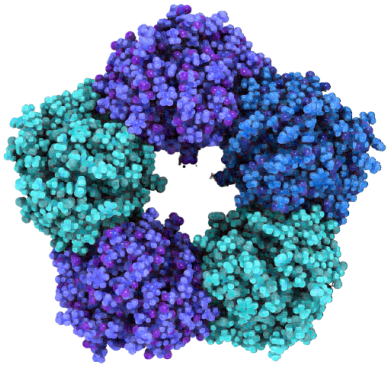
UNDERSTANDING

CRP's impact on cognitive health.

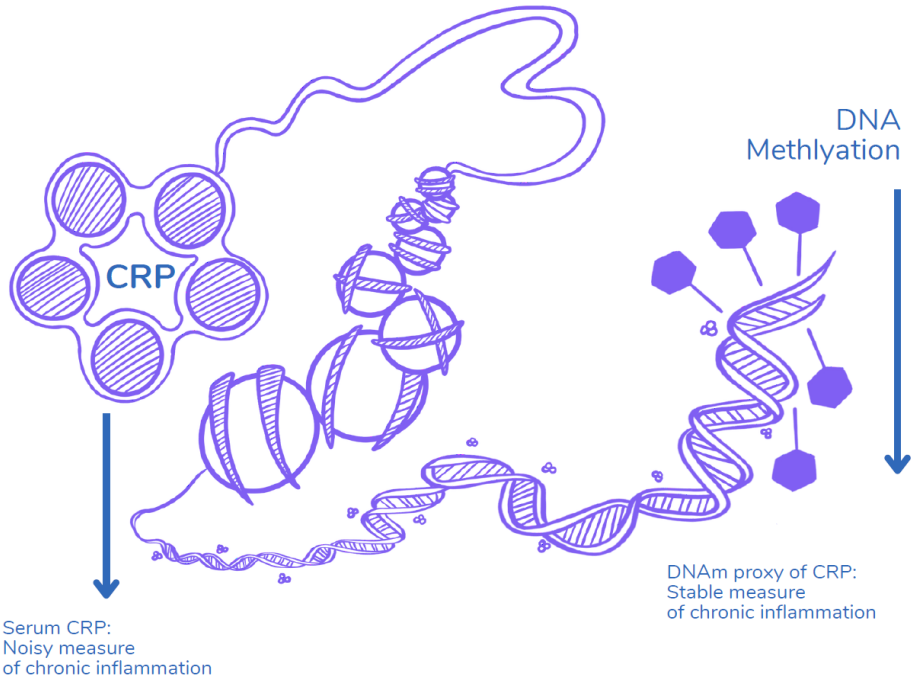
The liver produces CRP in response to acute inflammation. Healthcare providers use CRP measurements to indicate inflammation for various health conditions.

Elevated CRP levels are found to be associated with **low initial memory and verbal fluency** scores. Baseline inflammatory status is quantifiable by both peripheral inflammation-serum C-reactive protein (CRP) and an epigenetic measure methylation signature of CRP (DNAm CRP). However, DNAm has benefits over traditional measures.

One study conducted by Conole et *al* found that DNAm CRP is associated with total **brain volume**, (β = -0.197, 95% confidence interval [CI] -0.28 to -0.12, p FDR = 8.42 × 10-6), **gray matter volume** (β = -0.200, 95% CI -0.28 to -0.12, p FDR = 1.66 × 10-5), and **white matter volume** (β = -0.150, 95% CI -0.23 to -0.07, p FDR = 0.001).



Visualization of the CRP protein



JANE DOE | ID # ABC123

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TEST NAME: Inflammation Report

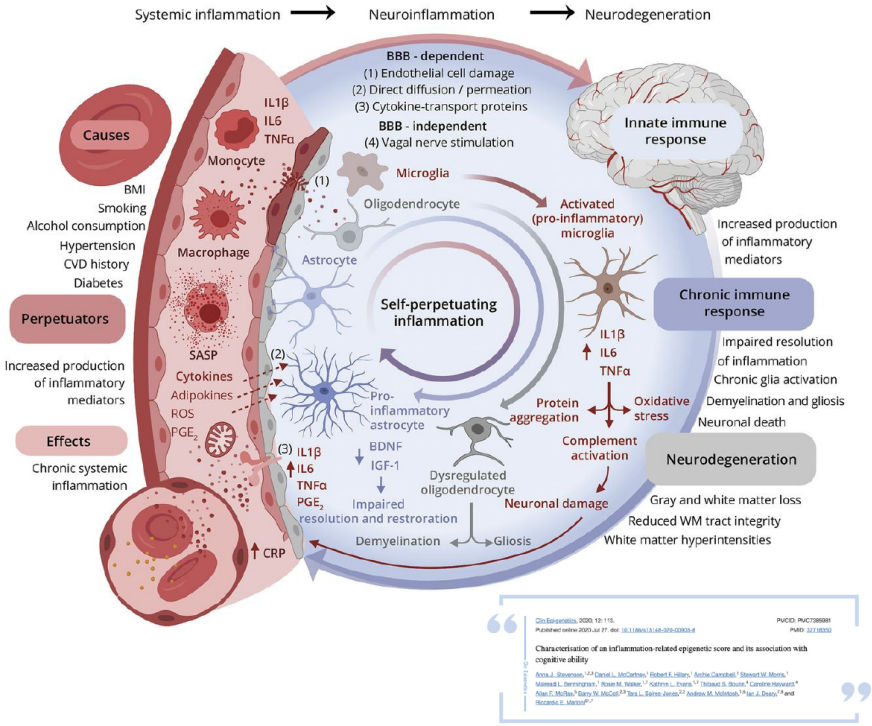
PRECISE & INFORMATIVE

Measuring CRP through DNAm.

DNAm CRP has emerged as a more precise bio-measurement than traditional CRP quantification and shows significantly **stronger associations with brain health outcomes** like chronic inflammation, brain structure, and cognitive functioning, compared to serum CRP measurements (on average **6.4-fold**). DNAm CRP has an inverse relationship with cognitive functions such as memory, speed, and visuospatial functions.

Only recently has there been a push for integrated multi-omics approaches to better characterize chronic inflammation. DNAm profiles may act as promising peripheral biomarkers for cognitive–aging differences at the population level, given their relative stability in the short term, and their **joint modulation by both genetic and lifestyle traits**. Elsewhere, DNAm markers of inflammation have proved informative in predicting a range of age-related health outcomes, from cardiovascular disease to depression, however, few studies have applied this same approach to cognitive aging differences in healthy cohorts.

As chronic inflammation is considered to be an insidious, cumulative, and often undetected contributor to cognitive aging, the importance of such epigenetic markers may be their **utility to index inflammatory load with greater reliability than phasic protein measures**.



Characterisation of an inflammation-related epigenetic score and its association with cognitive ability

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TEST NAME: Inflammation Report

UNDERSTANDING

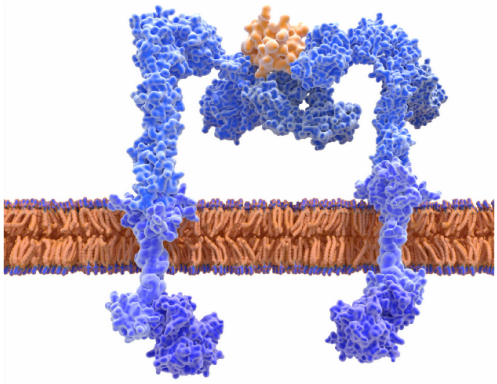
IL-6's impact on cognitive health.

Interleukin-6, also known as IL-6, is a pleiotropic, pro-inflammatory cytokine and is a principal stimulator of various acute-phase inflammatory proteins, such as CRP. IL-6 is a widely used marker of inflammation and circulating **levels of the cytokine typically rise with age.** On average, males show higher scores compared to women.

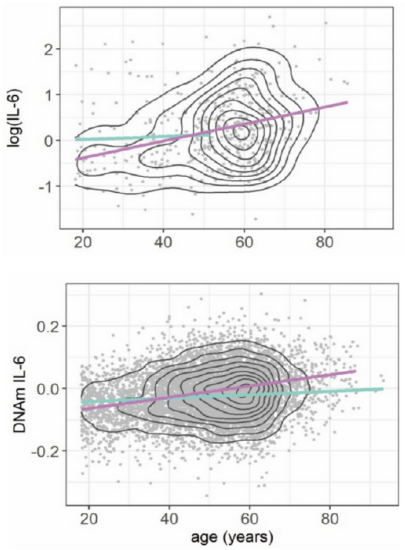
IL-6 is thought to be the transitionary biomarker, swinging from an acute, beneficial response to a chronic, deleterious state of inflammation. The DNAm IL-6 score created by Stevenson *et al.* was found to increase with age and is **negatively associated with cognitive function** (β = −0.19, SE = 0.07, pFDR = .014).

Research indicates that traditional IL-6 measures may be an unreliable predictor of chronic inflammation when focusing on temporal variability. Additionally, **DNAm IL-6 is able to track alterations in cell proportions** more directly than serum IL-6.

DNAm IL-6 measures have associations with sex, BMI, social deprivation, alcohol intake, and smoking status, while traditional IL-6 is typically just associated with increasing age. Of these known associations, DNAm IL-6 is positively associated with BMI, self-reported smoking status, and alcohol intake.



Visualization of the IL-6 protein



As noted in the graphs to the left by Stevenson et *al.*, both serum IL-6 and DNAm IL-6 were found to increase with age (**serum IL-6:** β = 0.022, SE = 0.004, p = 1.3 × 10−7; **DNAm IL-6 score:** β = 0.015, SE = 0.0009, p < 2 × 10−16).

Interestingly enough, males were found to have higher DNAm IL-6 scores compared to females (β = 0.25, SE = 0.02, p < 2 × 10−16).

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GENDER: XX	RECEIVED: 01-Mar-2023		
AGE: XX	TESTED: 01-Mar-2023		XXXXXXXXXXXXXXXXXXX

TEST NAME: Mitotic Clock Report

YOUR MITOTIC CLOCK REPORT

And The Epigenetic Timer Of Cancer

TruDiagnostic™ The Epigenetic Company

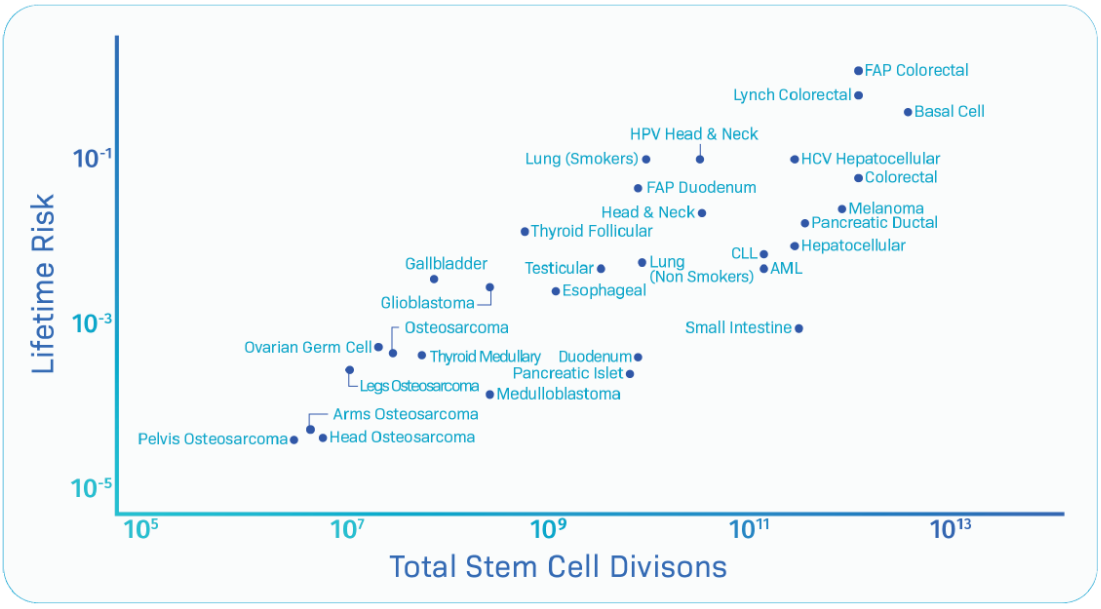
The link between cellular replication and cancer: **The "Bad Luck" Hypothesis**

Some tissue types give rise to human cancers millions of times more often than other tissue types. For example, the lifetime risk of being diagnosed with cancer is 6.9% for lung, 1.08% for thyroid, 0.6% for brain and the rest of the nervous system, and 0.003% for pelvic bone.

Some of these differences are associated with well-known risk factors such as smoking, alcohol use, ultraviolet light, or human papilloma virus (HPV). However, such exposures cannot explain why cancer risk is so vastly different in different tissues. Cancers of the small intestinal epithelium are three times less common than brain tumors, even though small intestinal epithelial cells are exposed to much higher levels of environmental mutagens than are cells within the brain, which are protected by the blood-brain barrier. Therefore, the main driver is probably not environmental exposures.

Another well-studied contributor to cancer is inherited genetic variation. However, only 5 to 10% of cancers have a heritable component, and even when hereditary factors in predisposed individuals can be identified, the way in which these factors contribute to differences in cancer incidences among different organs is difficult to determine. Therefore, genetics are probably not the main driver.

A study by Andrew Teschendorff, PhD found that inflammatory conditions also increased mitotic rates in tissue (Teschendorff 2020). ***Increased mitotic rates measured with this algorithm could also indicate stem cell depletion.***



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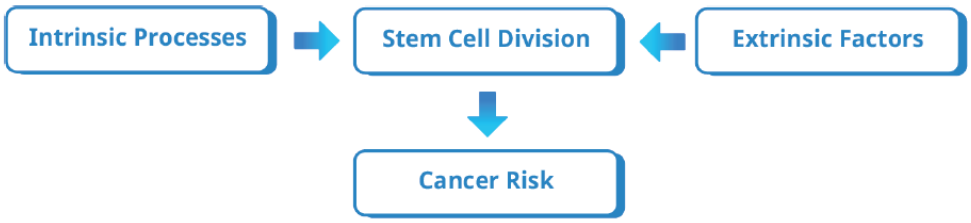
TEST NAME: Mitotic Clock Report

If hereditary and environmental factors cannot fully explain the differences in organ-specific cancer risk, how else can these differences be explained?

In 2016, a paper tried to explain why cancer risk is so different in some tissues than others. The research done by a group at Johns Hopkins (Tomasetti, Et. al), showed that the lifetime risk of cancers of many different types is strongly correlated (r2=0.81) with the total number of divisions of the normal self-renewing cells maintaining that tissue's homeostasis.

These results suggest that only a third of the variation in cancer risk among tissues is attributable to environmental factors or inherited predispositions. The rest is due to the "Bad Luck Hypothesis". This hypothesis points out that your cells are statistically more likely to make mistakes while copying DNA when they are replicating more often. As these mistakes accumulate, they can lead to cancer. Unfortunately, some of us just have bad luck and have more of these (intrinsic) errors than others.

"Intrinsic processes" include those that result in mutations due to random errors in DNA replication. "Extrinsic factors" are environmental factors that affect mutagenesis rates (such as UV radiation, ionizing radiation, and carcinogens).



How do I know how many stem cell divisions I have?

Cells replicate in a process called mitosis, where the DNA is fully copied during cell division. This process is fundamentally important to our survival, since cell replication is necessary for growing, healing and repairing our tissues. As time passes we end up creating trillions of cells, each with a tiny risk of making a mistake during cell division. With each small mistake our risk of cancer also slowly increases.

So how do we measure how much our cells are turning over? With epigenetic based mitotic clocks.

The Mitotic Clock score is estimated by looking at 385 locations (PCGT/PRC2-marked promoter CpGs) that are unmethylated at birth, but gain DNAm as chronological age increases. The algorithm to sort through this data was trained on a large cohort of healthy individuals, as assessed in one tissue type (blood). You can read the algorithm itself below.

$$TNSC(s) = \frac{1}{n}\sum_{i=1}^{n} w_i \beta_{is} = \frac{1}{n}\sum_{i=1}^{n} \frac{2\,\beta_{is}}{\delta_i}$$

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PATIENT: XXXXXXXXXXXXXXX			TEST REF: GNL-NL-XXXXX
TEST NUMBER: G-NL-XXXXXXX	COLLECTED: 23-Mar-2023		PRACTITIONER: SSSSSSSSSSS
GENDER: XX	RECEIVED: 01-Mar-2023		
AGE: XX	TESTED: 01-Mar-2023		XXXXXXXXXXXXXXXXXXX

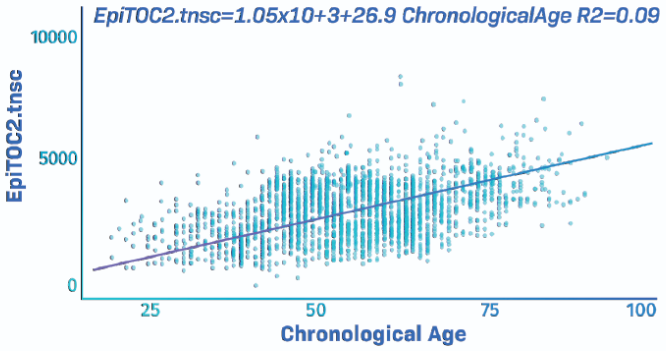
TEST NAME: Mitotic Clock Report

YOUR RESULTS:

Your ***cumulative number of stem cell divisions*** per stem cell per year:

3001

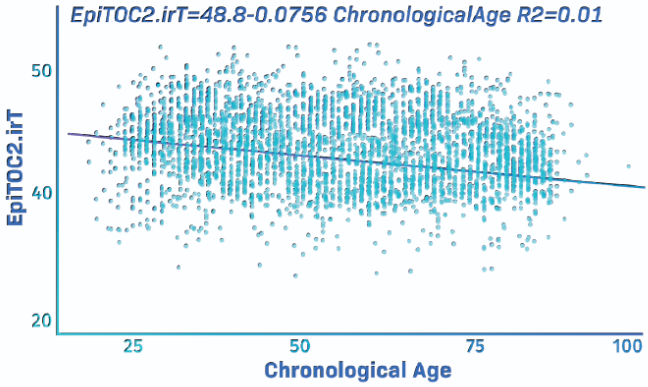
Based on your results, you would be in the **60th** percentile of Cell Division compared to others of your same chronological age.



Your ***median estimate for the intrinsic rate of stem-cell division*** for the tissue:

4004

Based on your results, you would be in the **70th** percentile of intrinsic rate of stem-cell divison compared to others of your same chronological age.



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TEST NAME: Mitotic Clock Report

WHAT DOES THIS MEAN FOR ME?

The Impact To You

It is important to note that this report **does not detect cancer.** This algorithm has been trained to predict the amount of stem cell division in tissue samples. While tissue turnover is generally correlated with increased risk of cancer, It is NOT a definitive diagnostic.

A study by Andrew Teschendorff found that inflammatory conditions also increased mitotic rates in tissue. Increased mitotic rates measured with this algorithm could also indicate stem cell depletion.

Still, it does highly correlate to cancer development **risk.** The mitotic clock exhibits age acceleration in normal buccal tissue from smokers compared with nonsmokers, and in normal breast tissue from patients with cancer compared with healthy women, making it aunique biological clock for estimating cancer risk.

If you are reading **exceptionally high** in this category, we would encourage you to pay special attention to getting regularly examined for any health issues with your physician.

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TRUAGE BY TRUDIAGNOSTIC

Fitness

This report measures how physical fitness impacts biological age and accelerated biological aging, by examining associated methylation patterns at various locations of your DNA.

Developed By TruDiagnostic's Bioinformatics & Research Department

A NEW AGING ALGORITHM

How your physical fitness impacts age.

It is a visible and well-known fact that physical fitness declines as we age. This functionality and performance loss is well-correlated with health, and can be measured indirectly through reduced function in specific organs (such as the lungs), as well performance tests of strength.

The rate and extent of this decline varies between individuals, however, **those who maintain physical fitness as they age are at lower risk for a range of diseases**. These people also tend to live longer lives.

The use of DNA methylation (DNAm) has allowed for the development of fitness biomarkers, as well as biomarkers of age-related changes in physical fitness. Physiological data can be incorporated into algorithms in order to **predict aging-related morbidity, disability, and mortality** through DNAm biomarkers; indicating that individual differences in various fitness parameters can be reflected in DNAm data.

The incorporation of physical fitness measurements into epigenetic clocks **increases the measurable effects of lifestyle, medical, and environmental interventional changes** on the aging process. The DNAmFitAgeAccel algorithm, also simply known as FitAgeAcceleration, was developed by researchers at UCLA, and is an estimate of epigenetic age acceleration. We have created a version of this, however, we incorporated our OMICm Age algorithm (developed with Harvard) instead. We call this **OMICm FitAge**, which tells you how old you are according to your physical fitness and functionality.

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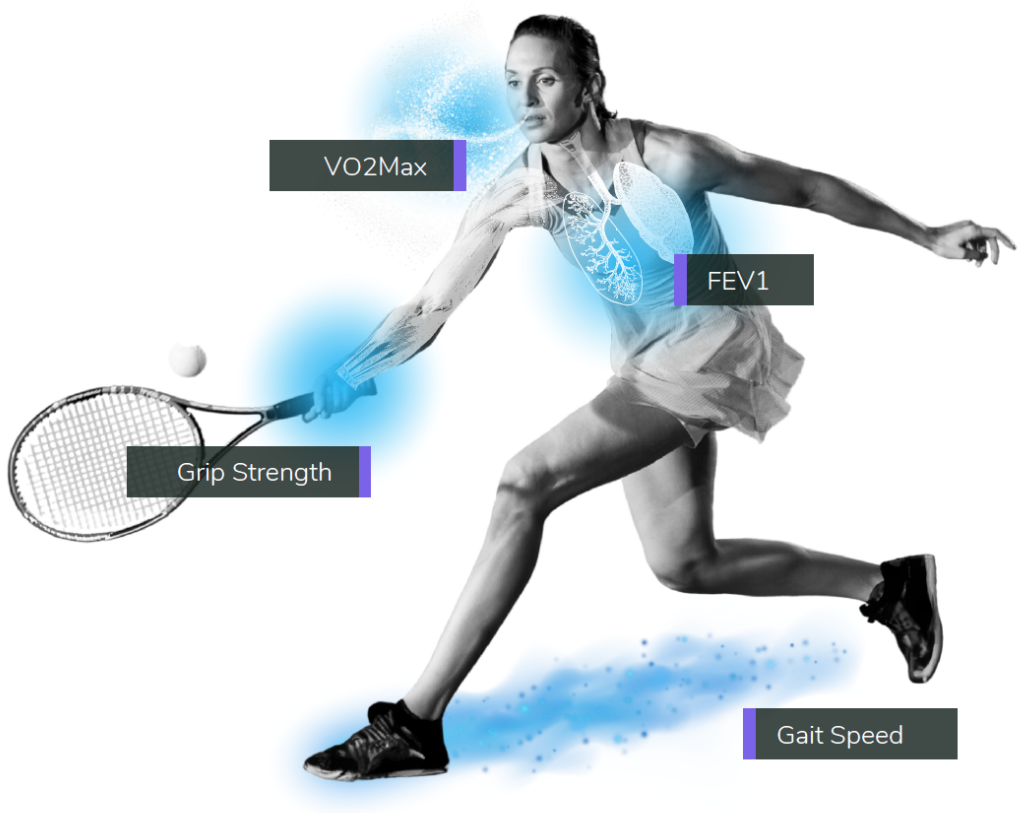
PATIENT: XXXXXXXXXXXXXX
TEST NUMBER: G-NL-XXXXXXX
GENDER: XX
AGE: XX

COLLECTED: 23-Mar-2023
RECEIVED: 01-Mar-2023
TESTED: 01-Mar-2023

TEST REF: GNL-NL-XXXXX
PRACTITIONER: SSSSSSSSSSS
XXXXXXXXXXXXXXXXXXX

TEST NAME: Fitness Report



VO2MAX

Maximal oxygen uptake, or VO2Max, is a measure of cardiovascular health and aerobic endurance. It measures **the volume of oxygen the body processes** during incremental exercise, in milliliters used in one minute of exercise per kilogram of body weight (mL/kg/min). DNAmVO2Max can be measured by blood to provide an epigenetic calculation of one's physical fitness. Highly fit individuals, as classified by VO2Max scores, are correlated with having a lower BMI and a higher GripMax (grip strength).

GRIP STRENGTH

Maximum hand grip strength (GripMax) is a measurement of force (taken in kg), and is used to calculate the age-associated decline in terms of **muscle strength**. Evidence suggests that grip strength may be a predictor of all-cause and disease-specific mortality, future function, bone mineral density, fractures, cognition and depression, and problems associated with hospitalization.

FEV1

Forced Expiratory Volume, also known as FEV1, measures **lung function** by determining the amount of air that is forced from the lungs in one second. DNAmFEV1 is a strong predictor of mortality and comorbidities.

GAIT SPEED

Gait speed, also known as **walking speed**, is measured in meters-per-second, and can fluctuate based on ones fitness level, the type of terrain, and how much effort is used. Muscle strength, especially in your lower body and hip flexors, also affects gait speed. Gait speed significantly and cumulatively decreases as your age increases, however, smaller declines are often associated with each year that age increases. This averages out to a difference of 1.2 minutes slower for every kilometer at age 60, than at age 20. Both men and women have a walking speed that stays fairly consistent until reaching their 60s, which is when it starts to decline considerably.

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AGE: XX

COLLECTED: 23-Mar-2023
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TESTED: 01-Mar-2023

TEST REF: GNL-NL-XXXXX
PRACTITIONER:
SSSSSSSSSSS
XXXXXXXXXXXXXXXXXXX

TEST NAME: Fitness Report

PROVIDED BY: TruDiagnostic™ The Epigenetic Company

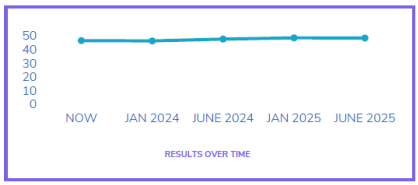
Your Results.

DISCLAIMER: All population graphs included in this report are based off of data from thousands of research participants and TruAge test takers. Population graphs are included to provide context to your results, with your individual scores being indicated by a neon green dot that is plotted amongst population trends.

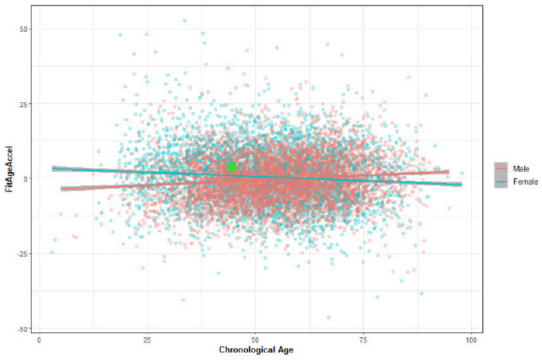
47.25
YEARS OLD
OMICm FitAge

Calendar Age
43.36

Fitness Age
47.25



Your OMICm FitAge is
HIGHER THAN
your calendar age by 4.25 years.



For every one year older that your OMICm FitAge is over your calendar age, there is an average **0.29 decrease in relative grip** strength and a 0.32 increase in BMI. OMICm FitAge has estimated that highly-fit individuals (classified through VO2max) have a **1.5 to 2.0 younger biological age** compared to low/medium fit individuals in females and males, respectively.

Younger OMICm FitAge was associated with better memory test performance, emphasizing the **beneficial role of physical exercise on cognitive health**.

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PATIENT: XXXXXXXXXXXXXXX			TEST REF: GNL-NL-XXXXX
TEST NUMBER: G-NL-XXXXXXX	COLLECTED: 23-Mar-2023		PRACTITIONER: SSSSSSSSSSS
GENDER: XX	RECEIVED: 01-Mar-2023		
AGE: XX	TESTED: 01-Mar-2023		XXXXXXXXXXXXXXXXXXX

TEST NAME: Fitness Report

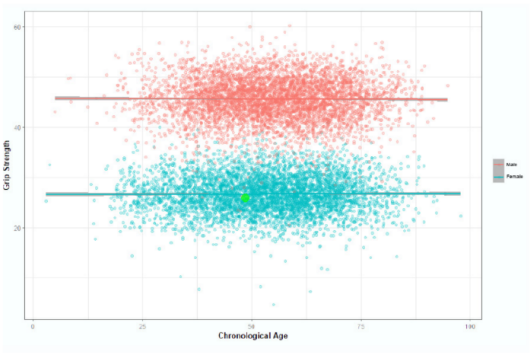
Your **Gait Speed** epigenetic biomarker proxy is higher than **47%** of the population with a similar reported age and sex.

Lower gait speed is associated with impairment of daily activities, physical inactivity, and cardiovascular disease.

Faster gait speeds indicate greater mobility- which helps to prevent disability, disease, and loss of autonomy.

Your Gait Speed epigenetic biomarker proxy score score is 1.7.

Your **Grip Strength** epigenetic biomarker proxy is higher than **28%** of the population with a similar reported age and sex.



Higher levels of Gripmax (DNA methylated Grip Strength) are associated with better verbal short-term memory; which is further associated with decelerated aging.

However, traditional grip strength measurements are correlated with overall strength, upper limb function, bone mineral density, fractures, falls, malnutrition, cognitive impairment, depression, sleep problems, diabetes, multimorbidity, and **quality of life**.

Your Grip Strength epigenetic biomarker proxy score 28.

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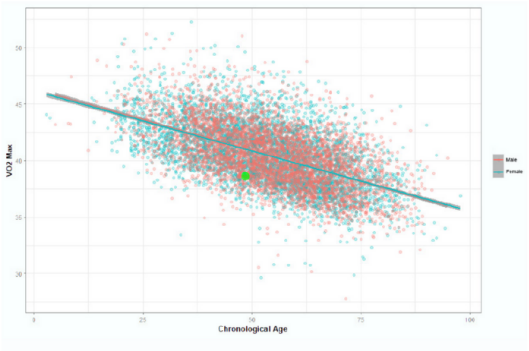
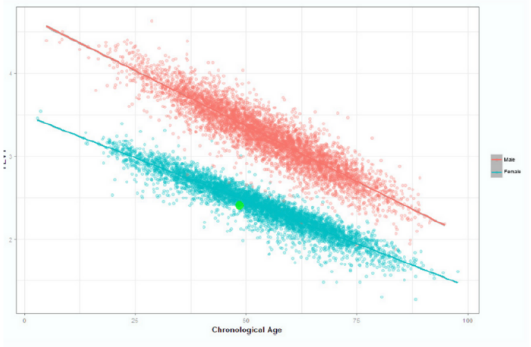
TEST NAME: Fitness Report

Your **V02MAX** epigenetic biomarker proxy is higher than **38%** of the population with a similar reported age and sex.



Your V02Max epigenetic biomarker proxy score is 38.

Your **FEV1** epigenetic biomarker proxy is higher than **32%** of the population with a similar reported age and sex.



Your FEV1 epigenetic biomarker proxy score is 2.86.

Higher levels of VO2Max is associated with better, verbal short term memory. Highly fit individuals, as considered by VO2Max levels, are associated with younger *OMICm FitAge* and lower BMI.

FEV1 specifically measures lung function. Collectively, these parameters make-up spirometry testing, which is beneficial in diagnosing chronic obstructive pulmonary disease (COPD), asthma, restrictive lung disease, and other disorders that affect lung function. In addition, **VO2Max and FEV1 are predictive of mortality.**

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TRUAGE BY TRUDIAGNOSTIC

Smoking & Disease Risk

This report explores the impacts of smoking habits on biological age and accelerated biological aging by examining associated methylation patterns at various locations of your DNA.

Developed By TruDiagnostic's Bioinformatics & Research Department

UNDERSTANDING

How smoking status & history influence disease risk.

Cigarette smoking is one of the leading causes of preventable disease, disability, and death in the United States, accounting for more than 480,000 deaths every year. Tobacco use accounts for 7 million deaths globally. In 2020, nearly 12.5% of adults in the U.S. currently* smoked cigarettes. More than 16 million Americans live with smoking-related diseases like cancer, heart disease, diabetes, COPD, and more.

***As per the CDC, current smokers are defined as people who reported smoking at least 100 cigarettes during their lifetime and who reported smoking every day or some days.**

GENE: AHRR cg05575921

EPIGENETIC STATUS

- Altered when exposed to toxins from tobacco smoke

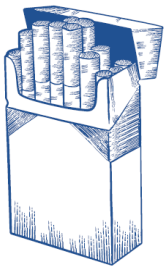
HYPOMETHYLATION OF AHRR

- Reduced AHR clearance of toxin
- Increased plaque/fat build-up in arteries

HYPOMETHYLATION OF AHRR cg05575921

- Associated with smoking + CVD

This gene has the highest level of DNA methylation change in response to smoking status.



SMOKING & DNA METHYLATION

Smoking leaves a long-term signature on DNA methylation of its exposure and is one mechanism that tobacco exposure predisposes many to adverse health outcomes. Researchers have found that CpG loci are enriched with associations of several smoking-related characteristics that contribute to damaging outcomes to health, making epigenetics a promising indicator for the impact smoking exposure has on genome-wide methylation.

Smoking inhalation can still be considered a risk factor for almost all people. Researchers have concluded that high levels of second-hand smoke exposure are inversely associated with DNA methylation of AHRR cg05575921 in blood cells from nonsmokers.

SMOKING & DNA METHYLATION

A hazard ratio (HR) is the probability of events in a treatment group (individuals who have smoked) compared to the probability of events in a control group (individuals who have never smoked) and it determines the ratio for the probability of being diagnosed with a certain condition.

(Figure 1) Individuals from the Copenhagen City Heart Study were grouped based on their methylation levels (quartiles) determined by their smoking status. The lowest quartile (1st) is associated with the highest percentage of active smokers at baseline while the highest quartile (4th) is associated with the lowest percentage of active smokers at baseline.

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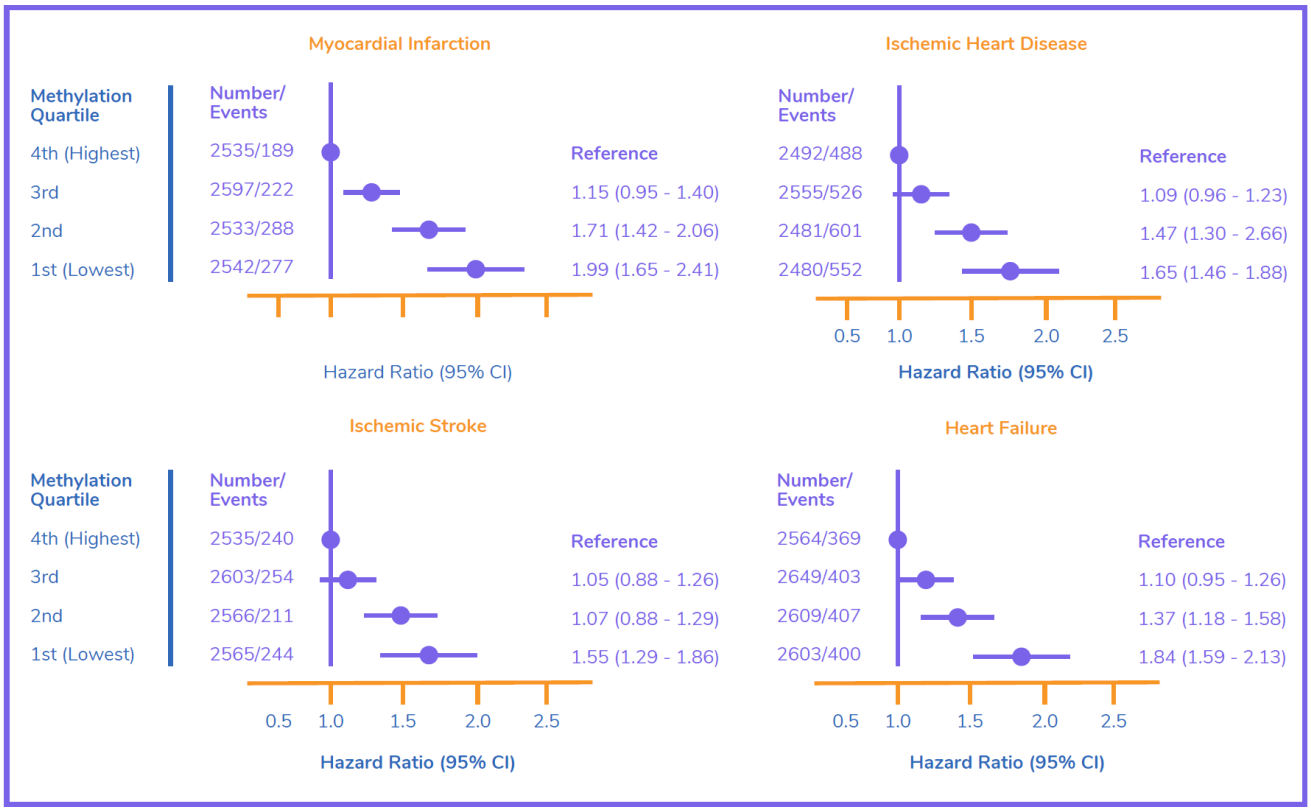
TEST NAME: Smoking and Disease Risk Report

FIGURE 1

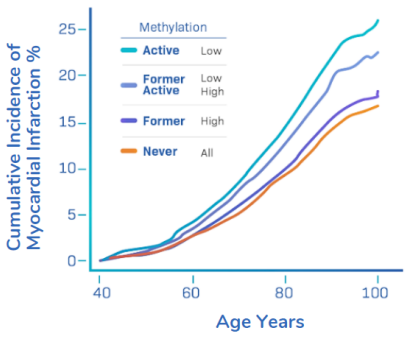


MYOCARDIAL INFARCTION

Myocardial infarction, commonly known as a heart attack, is caused by atherosclerosis, a condition where plaque builds up inside the arteries. Studies suggest measurement of AHRR cg05575921 hypomethylation is a **better marker of risk of myocardial infarction than self-reported smoking history**, even after adjusting for smoking status.

Langsted et al. conducted an 18-year follow-up of the Copenhagen City Heart Study, and approximately 1,000 incidences of myocardial infarction events occurred. The cumulative incidence of myocardial infarction **increased with age but was lowest in never-smokers and highest in active smokers with the lowest degree of methylation** (Figure 2).

FIGURE 2



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PATIENT: XXXXXXXXXXXXXX
TEST NUMBER: G-NL-XXXXXXX
GENDER: XX
AGE: XX

COLLECTED: 23-Mar-2023
RECEIVED: 01-Mar-2023
TESTED: 01-Mar-2023

TEST REF: GNL-NL-XXXXX
PRACTITIONER:
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XXXXXXXXXXXXXXXXXXX

TEST NAME: Smoking and Disease Risk Report

AGING

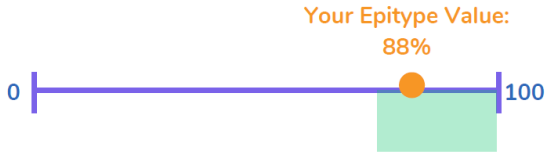
Although smoking is known to increase biological age by 5 to 7 years, promising insights have determined that smoking cessation may reduce biological age.

A pilot investigation of the impact of smoking cessation on biological age-tested smokers who averaged at baseline 13 cigarettes a day. The researchers assessed the AHRR cg0557592 methylation status and found **that 3-4% demethylation occurred just after one month of smoking cessation.** The rapid and substantial reversal of accelerated aging associated with smoking cessation supports that reversal of biological age of a former smoker.

Another study conducted by Wu et al., showed that smoking increased the epigenetic age of airway cells by **an average of 4.9 years and lung tissue by 4.3 years.** After smoking ceased, the epigenetic age acceleration in airway cells (but not in lung tissue) slowed to a level that non-smokers had. Patients who quit smoking, heavy smokers included, appeared biologically younger than they were at baseline. The connection between aging, smoking, and cessation serves as a powerful incentive for patients to quit smoking.

Your Results.

AHRR (cg05575921)
Average Beta Value %:



[64%-100%]
No Epigenetic Risk

The impact that tobacco smoke exposure has on the epigenome is based on the level of methylation at the AHRR gene locus cg05575921.

Your DNA methylation score was 88% at the AHRR locus, meaning that your methylation score aligns with the status of non-smokers, putting you at low risk for developing smoking-related conditions.

TREATMENT

It has been noted that specific genes, such as AHRR, exhibited a reversal of DNA methylation changes in ex-smokers who quit smoking at least 10 years prior to collecting their sample. 10 years+ post-cessation, as seen in Figure 2, **leads to a reversal in DNA methylation at AHRR**, resulting in methylation levels similar to those observed in never-smokers.

By limiting tobacco exposure, hypomethylation at the AHRR gene will reduce, decreasing the chance of smoking-related diseases. The longer the time since cessation, the more likely the epigenome will revert back to the healthy methylation levels.

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PATIENT: XXXXXXXXXXXXXX			TEST REF: GNL-NL-XXXXX
TEST NUMBER: G-NL-XXXXXXX	COLLECTED: 23-Mar-2023		PRACTITIONER: SSSSSSSSSSS
GENDER: XX	RECEIVED: 01-Mar-2023		
AGE: XX	TESTED: 01-Mar-2023		XXXXXXXXXXXXXXXXXX

TEST NAME: Alcohol Consumption Report

TRUAGE BY TRUDIAGNOSTIC

Alcohol Consumption

This report explores the impacts of alcohol consumption habits on biological age and accelerated biological aging by examining associated methylation patterns at various locations of your DNA.

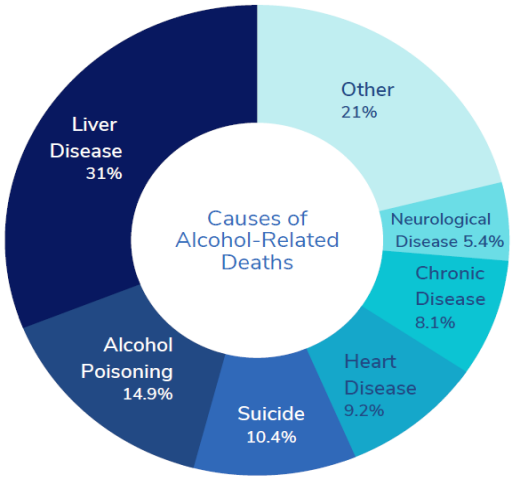
Developed By TruDiagnostic's Bioinformatics & Research Department

UNDERSTANDING

What alcohol does to my biology.

Drinking alcohol is a major lifestyle risk factor contributing to the worldwide burden of chronic disease and death. Modest alcohol use may increase disease risk, but **the greatest risks are observed in chronic drinking**.

Excessive alcohol consumption, over time, can lead to long-term health risks. As the CDC explains, these chronic diseases include alcohol-related hypertension, liver disease, cancer, dementia, alcohol use disorder, and more.



With the help of epigenetics, we can understand how our lifestyle behaviors, such as drinking, affect gene expression. This report looks at the **methylation markers leftover from alcohol consumption**.

These markers appear to be reversible after time spent abstaining from drinking, but do take substantial time to reflect those changes. Therefore, heavy drinking several years ago followed by recent abstinence may show up as a light drinker, despite having no alcohol consumed at all within the last year.

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COLLECTED: 06/01/2020 | REPORTED: 07/01/2020

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PATIENT: XXXXXXXXXXXXXX			TEST REF: GNL-NL-XXXXX
TEST NUMBER: G-NL-XXXXXXX	COLLECTED: 23-Mar-2023		PRACTITIONER: SSSSSSSSSSS
GENDER: XX	RECEIVED: 01-Mar-2023		
AGE: XX	TESTED: 01-Mar-2023		XXXXXXXXXXXXXXXXXX

TEST NAME: Alcohol Consumption Report

UNDERSTANDING

How alcohol speeds up my biological aging.

SLEEP

Sleep is crucial for cellular regeneration. Alcohol intake disrupts sleep and thus interferes with your body's ability to produce new, healthy cells; accelerating your biological aging processes. Over time, this disruption can affect physical appearance, as well as decrease cognitive function.

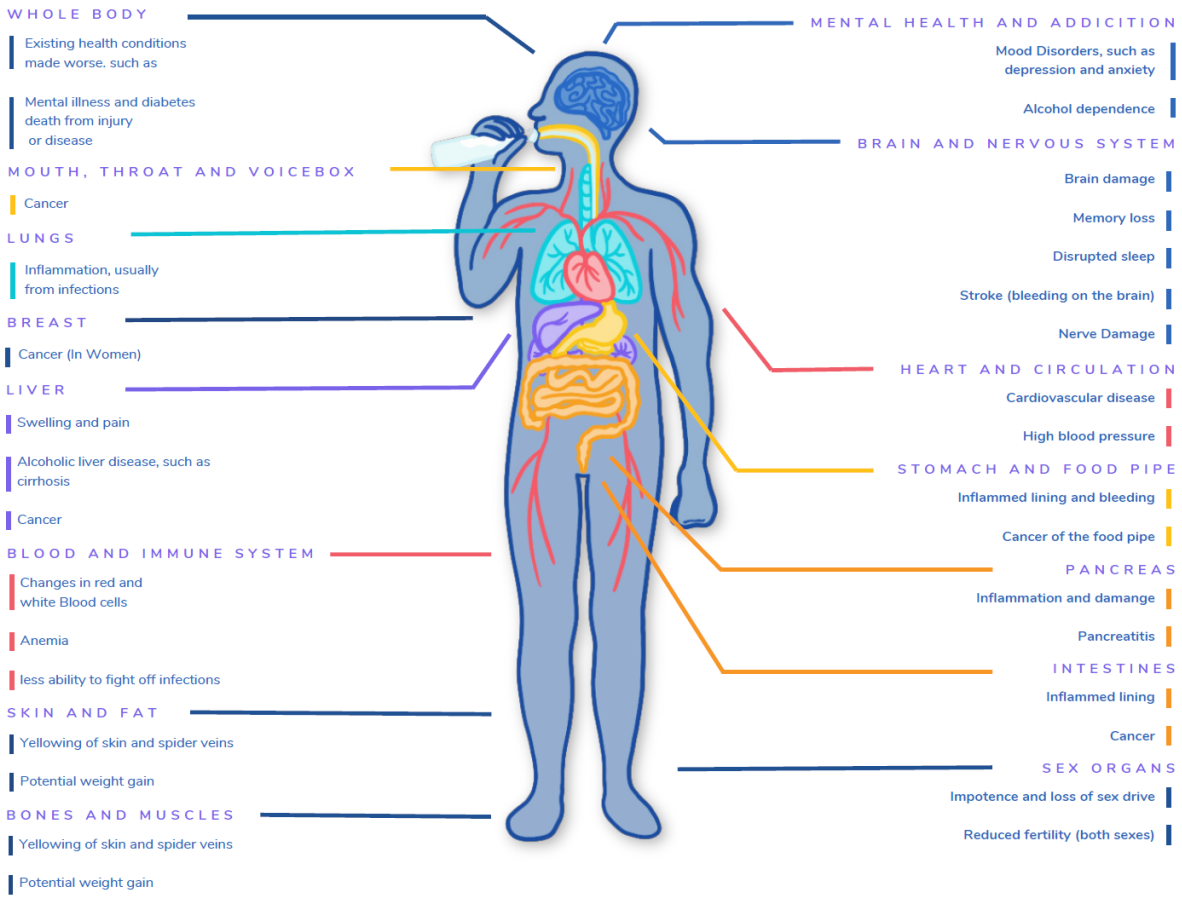
SKIN

Drinking alcohol causes dehydration and depleted levels of vitamin A and collagen; both of which notably decline with age. This can lead to premature wrinkling of the skin and loss of elasticity.

BLOOD & LIVER

Accelerated biological aging has been observed in blood and liver tissue samples, but not in brain tissue. Studies show that epigenetic aging differs in the blood and liver tissue of individuals with alcohol dependence compared to healthy volunteers. Excessive alcohol consumption may be associated with epigenetic aging in a tissue-specific manner.

LONG-TERM HEALTH EFFECTS OF DRINKING ALCOHOL



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TEST NAME: Alcohol Consumption Report

UNDERSTANDING

My data & results.

DNA Methylation is a robust biomarker that provides significant detection of past and current alcohol intake, and substantially out performs many other biomarkers for detecting the impacts of heavy alcohol drinking. Analysis of the epigenome in drinkers and former drinkers has identified **over 140 locations on your DNA related to habitual drinking**.

Lifestyle, medical, and environmental factors affect how, where, and to what degree DNA methylation occurs. These known factors include drinking, nutrition, chronic or acute stress, sleep habits, activity levels, inflammation, oxidative stress, and hypoxia. Although not permanent, **reducing these factors can reverse patterns of methylation**.

Associated genes we looked at:

SFRS13A | ANP32B | CPNE1 | TAF1D
STAM2 | GPT2 | SLC1A5 | FAM49A
PRELP | ANKRD1 PRDM10 | NFIX
CHD2 | RBM26 | SNX5

JANE,

your risk of alcohol consumption impacting how your DNA is expressed, and accelerating your biological aging is

HIGHER THAN 30%

of the tens of thousands of patients we have tested.

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PATIENT: XXXXXXXXXXXXXX
TEST NUMBER: G-NL-XXXXXXX
GENDER: XX
AGE: XX

COLLECTED: 23-Mar-2023
RECEIVED: 01-Mar-2023
TESTED: 01-Mar-2023

TEST REF: GNL-NL-XXXXX
PRACTITIONER: SSSSSSSSSSS
XXXXXXXXXXXXXXXXXXX

TEST NAME: Alcohol Consumption Report

Your Results.

Do you ever wonder why many older adults experience a harder time battling diseases like COVID-19 or the flu, compared to younger people who typically have an easier time recovering from the same illnessess boils down to the capabilities of one's immune cells to effectively respond to internal and foreign health threats; capabilities which tend to decrease with age. This age-related decline of the immune response in our blood is called immunosenescence.

ADDING CONTEXT TO

Your drinking score.

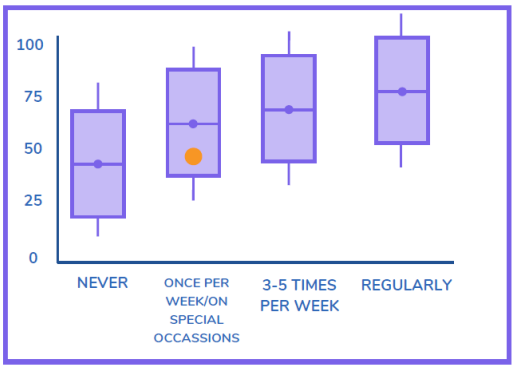
The methylation markers we look for appear quickly in response to alcohol consumption, and heavy drinking in the past two months can rapidly increase an individual's drinking status.

Methylation on these DNA locations for women tend to be more sensitive to alcohol consumption than for men.

You reported your drinking status to be **RARELY OR ONCE WEEKLY.**

Your biology more closely resembles alcohol impacts among people who **NEVER DRINK.**

Alcohol Consumption and DNA Methylation



The methylation risk percentile is a measurement of your drinking behavior, based on changes we see in the epigenome from alcohol consumption. With this method of comparison, people who consume alcohol often have higher scores overall; meaning they experience greater biological and aging impacts directly tied to drinking.

On your intake survey, you self-reported your drinking status as RARELY OR ONCE WEEKLY. In the graph above, you can see how your self-reported drinking relates to these methylation scores.

With our custom methylation risk score, you are in the 30th percentile. This means the impact of alcohol consumption on your DNA expression is higher than 30% of our tested population.

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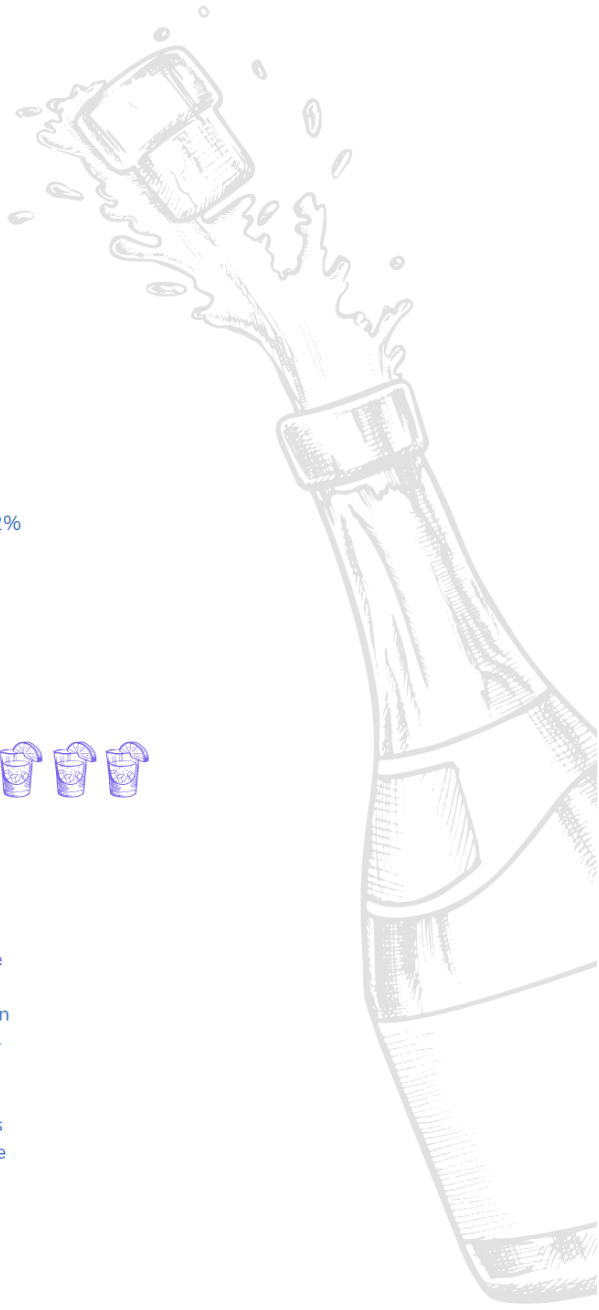

UNDERSTANDING

What I can do to improve my score.

Scaling back on your alcohol consumption is an easy way to see improvements without the sometimes challenging commitment of abstaining from drinking all together.

In the U.S., one "standard" drink contains ≈14 gm of pure alcohol. This can look like a 12 oz, regular beer (5% alcohol), a 5 oz glass of wine (12% alcohol), or 1.5 oz of distilled spirits (40% alcohol). **Binge** and **Heavy Drinking** are considered too much.

BINGE DRINKING

Women: 4+ drinks per occasion
Men: 5+ drinks per occasion

HEAVY DRINKING

Women: 8+ drinks per week
Men: 15+ drinks per week

Studies have found that people who stop drinking alcohol completely, even if they had previously been a habitual and heavy user, **can reverse their methylation patterns to eventually match the group who never drank at all**! However, some studies suggest this process of methylation reversal could take more than 10 years for cases of excessive and long-term alcohol abuse.

The good news is that even a single year of abstaining from alcohol has shown positive effects on methylation patterns and corresponding gene expressions impacted by that methylation.

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EDUCATIONAL CONTENT

FAQs

TOP QUESTIONS

I have not drank at all in recent years OR I have never consumed alcohol in my entire life. Why do I have any methylation at all in this report?

The epigenetic locations we looked at for this report are most strongly impacted by alcohol consumption, however, methylation of these areas can naturally occur with age, regardless if alcohol consumption is increasing or expediting the methylation process.

EDUCATIONAL CONTENT

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TEST NAME: Weight Loss Report

CPG LOCI REPORT

TruDiagnostic™ The Epigenetic Company

IMPACT: Weight loss response to caloric restriction

GENES: PON3

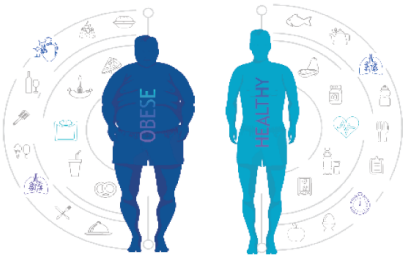
Weight Loss

Weight loss can be difficult, especially for individuals who have been overweight for years. There is not a one-size-fits-all approach to weight loss therapy. A hypocaloric (calorie-deficient) diet is typically considered one of the best approaches for weight loss, but not everyone responds to calorie deficit in the same way. Even with a strict regimen and no deviations, there are molecular and epigenetic components to how a body will respond to calorie deficit. Sometimes weight loss isn't a sure thing.

This report aims to help individuals identify their personal weight-loss response to caloric restriction.

YOUR EPITYPE:

Based on your methylation, you are a **non-responder** for weight-loss interventions using caloric restriction.



What is Obesity?

Obesity can be defined as a disease in which excess body fat has accumulated such that health may be adversely affected.
The prevalence of obesity has increased dramatically over the past few decades. It presents major health obstacles because of its substantial increase in risk for diseases such as type 2 diabetes, hypertension, myocardial infarction, stroke, dementia, osteoarthritis, and many types of cancer.

The rising incidence of obesity has caused the condition to be so common within the world's population that it is beginning to replace undernutrition and infectious diseases as the most significant contributor to ill health.

The global epidemic of obesity is fueled by a combination of genetic susceptibility, increased availability of high-calorie foods and decreased requirement for

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TEST NAME: Weight Loss Report

Analyzing DNA Methylation

Our laboratory uses array-based DNA methylation testing to identify sites where methylation has occurred and measure the degree to which that location has been methylated. Advances in the field of epigenetics have found that we can use these variations in methylation can identify changes in specific biological responses.
For each gene, there is a range of methylation statuses that are considered normal, and methylation that falls outside that range.

Hypomethylation is when the methylation status is below a specific threshold. This threshold depends on the CpG loci it's on. Hypomethylation is also what we call the process of a gene losing methylation.

Hypermethylation, is when a gene's methylation status is over a specific threshold. It can also be the process of gaining more methylation.
A hypermethylated gene is usually being repressed or silenced.

What are CpG Loci?

CpG loci are specific locations on your DNA where methylation can occur. They are often near sites that begin transcribing a gene's instructions so those instructions can be carried out by the body.
When methylation occurs on the loci around a gene, the instructions can be changed from their original meaning or silenced entirely. A single gene can be influenced by the methylation on many nearby CpG loci.
In this report, we examine how much methylation has occurred on CpG loci around specific genes, and offer insights into how those changes affect you.

What affects DNA Methylation?

We have not yet uncovered the full list of everything that can influence DNA Methylation development. Known factors include nutrition, chronic or acute stress, sleep habits, activity levels, inflammation, oxidative stress, hypoxia, and much more.

Many patterns of methylation are not permanant, and studies have found they can be reversed by interventions like reducing stress, improving nutrition, and reducing exposure to pollutants or biological stressors. Neither of these lists are comprehensive.

What are Beta Values?

A beta value is essentially the percent-value that a specific CpG loci has been methylated. Depending on how many methyl molocules attached to that CpG, the loci could be anywhere from 0% to 100% methylated.
The more methylation a CpG has, the more it's working to silence nearby genes.
While a single CpG that is 100% methylated generally cannot silence an entire gene, groups of highly methylated CpG can work together to do so.

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SSSSSSSSSSS
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TEST NAME: Weight Loss Report

Your CpG Beta Values

	CpG site	Gene	ß-value Responders	Your Score	Response Status
1	cg15500865	PON3	0.072	0.63	Hypermethylated
2	cg25161512	PON3	0.115	0.111	Hypomethylated
3	cg11435506	PON3	0.165	0.161	Hypomethylated
4	cg03301582	PON3	0.120	0.117	Hypomethylated
5	cg08898155	PON3	0.163	0.167	Hypermethylated
6	cg04080282	PON3	0.324	0.321	Hypomethylated
7	cg26457160	PON3	0.490	0.494	Hypermethylated
8	cg10329418	PON3	0.252	0.250	Hypomethylated
9	cg27166921	PON3	0.253	0.251	Hypomethylated
10	cg24750391	PON3	0.355	0.359	Hypermethylated
11	cg08461772	PON3	0.418	0.417	Hypomethylated

Possible Outcomes:

Non-Responder: CpG loci around your PON3 gene are generally under-methylated. Your response to caloric restriction alone is low, so it is not likely to be the most effective form of weight loss.

Intermediate Responder: CpG loci around your PON3 gene are in the normal range. Using a calorie deficit diet for weight loss may work, but it may not be as successful as other therapies.

Full Responder: CpG loci around your PON3 gene have been hypermethylated, so calorie restriction as a method of weight loss should be very effective.

Learn About Your Genes

PON3

PON3 creates a protein that circulates in the blood stream. This protein binds to lipoproteins, which transport fat molecules through the blood.

The PON3 protein protects lipoproteins like HDL and LDL (also known as cholesterols) against oxidation. When LDL is oxidized, it can cause inflammation which leads to plaque in the arteries and possible damage to arterial walls.

Oxidized LDL is also believed to play a role in increasing the amount of fat your body deposits. It increases the production of triglycerides, which is the most common type of fat produced when your body has extra calories available.

Studies have found that the pattern of methylation on PON3 can predict how a person's weight and body fat will respond to caloric restriction.

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TEST NAME: Weight Loss Report

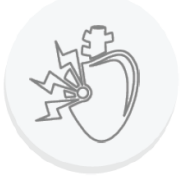


THE IMPACT ON YOU

CpG loci around your PON3 gene are generally under-methylated. Based on your methylation, you are a **non-responder** for weight-loss interventions. This means your response to caloric restriction alone is low, so it is not likely to be an effective form of weight loss.

Knowing the impact your gene expression has on your ability to treat weight management can help you and your healthcare provider determine the best interventions for weight loss in the future.





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