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What DNA Methylation Testing Can Tell You About Your Health

Analysis by Dr. Joseph Mercola ✔ Fact Checked

STORY AT-A-GLANCE -

- TruDiagnostic is a commercial testing system that determines your biological age, as opposed to your chronological age, by measuring your DNA methylation
- Your genes have promoter sites at the beginning of the DNA strand, and methylation is measured at those sites. The level of methylation at the promoter site correlates to the degree of expression of that particular gene
- Biological aging is a primary cause for chronic disease. If everyone in the world were to be seven years younger biologically than their chronological age, the global disease burden would be reduced by 50%
- Patients who contracted COVID-19 were found to have telomere length shortening, but while people over age 50 showed increased biological aging as a result of the infection, people younger than 50 had the converse effect, actually getting biologically younger
- Among the more exciting antiaging therapies now available are very small embryonic-like stem cells (Vsels), which have shown multiyear age reversals even after a single treatment. Other promising therapies are senolytics and plasma exchange apheresis

Ryan Smith is the founder of TruDiagnostic, a commercial testing system that tests your biological age, as opposed to your chronological age. It's can be a profoundly useful tool, because you need an objective barometer to tell you whether or not the things you're doing to improve your health are actually having the desired impact.

TruDiagnostic was founded in March 2020, right as the COVID pandemic hit, and the first commercial testing began in July that year. Since then, the company has launched more than 30 ongoing clinical trials, looking at a variety of interventions. They're also looking at how COVID-19 affects health metrics and longevity.

> *"We've built out new algorithms, new ways to read these DNA methylation markers that we measure for other functional health benefits,"* Smith says. *"DNA methylation is a really robust platform. But it's also very new. We even have ways to look at how much arsenic or heavy metals you've been exposed to over your entire life, how many plastics you've been exposed to.*
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> *If there's one thing to take away from this talk, I think it's that this epigenetic platform will change every area of medicine as a diagnostic, which is changeable, but also can tell us a lot about different areas of medicine and really fit a need that we don't have in a lot of diagnostics.*
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> *So, I'm very excited about the field, but particularly aging — how to quantify that process, and then hopefully how to reverse it so that we can have really good results on increasing people's health span and life span, making them not only live longer, but live a high-quality life as well."*

What Is DNA Methylation?

The idea of epigenetic methylation is rooted in the concept that every cell in your body has the exact same DNA, but express that DNA in very different ways. The cells of your skin do not express the same genes as your heart cells, for example.

We now know that the expression of genes is regulated, in part, epigenetically. As your cells differentiate into different types of tissues, they change their epigenetic expression to regulate what genes are turned on and turned off.

> *"I liken it to a light bulb. You can have an engineer look at a light bulb and tell you exactly what it's made for and how to turn it on, but if you don't know if it's*

on or off, then you're missing a big point of why it was created. It's the same with our cells.

This idea of measuring how things were turned on or turned off in our DNA expression has been known for a long time, but only recently scaled to a platform where we can actually investigate this on a large scale. So, what we measure is DNA methylation."

DNA methylation is the silencing of gene transcription. Your genes have promoter sites at the beginning of the DNA strand, and methylation is measured at those sites. The level of methylation at the promoter site correlates to the degree of expression of that particular gene.

"The converse process is a process called acetylation, which is a charged molecule which can open up those proteins to allow your genes to be transcribed [i.e., the turning on of the gene]. We measure specifically just that negative regulatory process, the DNA methylation," Smith explains.

What's being measured is not your ability to methylate or not methylate. Rather, it measures the actual expression of your DNA. And, contrary to conventional genetic testing like 23andMe, which is done once, DNA methylation can be measured multiple times as the actual expression of your DNA is alterable and changes over time.

"Due to advances with big data analysis and artificial intelligence, what we're able to do is take large scales of that data, so we can look at over 900,000 locations in your genome to see what the percentage of methylation is. Then we can correlate it to several different things."

DNA Methylation and Aging

Biological aging was one of the first things to be looked at using this platform because there was such a high correlation between DNA methylation and aging. Publications on this go back to 2009. In 2013, Dr. Steven Horvath created a chronological age-trained

methylation clock, which, with just a couple nanograms of DNA, could help determine how old, chronologically, an individual was. Ryan states:

> *"It elucidated this idea that aging, the aging process, can actually be quantified very, very accurately, but also might even be responsible for a lot of the health considerations we see with age.*
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> *It's important to note that aging is the No. 1 risk factor for all chronic disease and death. If there's one thing you could do in a lifestyle capacity to prevent the development of age-related diseases, it is to essentially not age.*
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> *So that's a goal, but it's also a very difficult one to measure and do, because chronological age has been our only measurement for this for some time. We all know people in their 70s who look like they're in the 50s. We all know people in their 50s who look like they're in their 70s. So, chronological age has never been the best measurement. This molecular measurement can give us a much better idea of how we're aging."*

The field of epigenetics is still in its infancy, and there are many fascinating areas of study underway. For example, there are already products on the market that are able to help diagnose up to 50 types of cancer from a single blood test.

Researchers are also looking senolytic clocks, which can be useful in the treatment of COVID, as they can tell you the overall burden of senescence in your body, and whether you might benefit from senolytic products.

How TruDiagnostic Compares to Other Companies

When asked how TruDiagnostic compares to other companies working with similar platforms, Smith replies:

> *"There are three things I like to draw attention to whenever I get asked that question. The first is the breadth of the measurement. With new clocks and new analyses coming out every day, one of the important things is making sure that*

you're measuring a lot of data, because as these new clocks or new algorithms come out, you want to be able to update them to make them even more accurate and more insightful.

So, one of the core tenets of what we wanted to do was to measure a lot of DNA. We measure over 900,000 locations. That is generally out of 26 million, approximately. So, it's still a very small amount of the total, but it's significantly more than any of our competitors, which might be measuring at most a 100,000.

So, we definitely like to scale because this is going to be a forward compatible platform. The human genome was only recently finished in terms of sequencing and the same will happen with epigenetic methylation, where, as we learn how to use this information, we'll be able to interpret it different ways.

We release new reports every three to four weeks with additional insights that are published in the literature. That way, we can keep everyone informed and up to date ... We want to provide any of our customers who do our test with the continuing updates.

Generally, even if someone did a test when we first started, they'll probably be getting updates for the next decade as we continue to see how this information and the ability to interpret it progresses ...

The next part of it is the algorithms piece, particularly the interpretation of that data. We only use published algorithms.

That is one of the things that we are very adamant about because otherwise, if you don't know how these measurements are related to health outcomes or related to different therapies, it's like taking the word of a fortune teller ... Publication is one of the main ways to have that scientifically valid and reliable measurement.

[Lastly], the important thing when you're taking these DNA methylation samples is the tissue that you're taking. We only use blood, the reason being is that most of these algorithms have been created off of blood samples. One of the interesting things about epigenetics is that every cell type is different.

If we were to measure your brain with the same algorithm we [used to] measure your blood, we would get much lower ages than we would on your blood. If we tested your breast tissue, for instance, we get much higher ages than if we tested your blood. So, the tissue type is very important, which is why we only use blood. Although it's not as easy to collect, it is definitely more scientifically reliable.

So, as you're evaluating which epigenetic companies to use, those would be my three criteria. Figure out the algorithms that they're using and reporting, make sure they're published, make sure they're measuring a good number of locations in case you want to know anything about that sample in the future.

Then lastly, make sure that they're using a collection method that has been validated in the literature, which mainly at this point is either blood or skin."

DNA Methylation Versus Telomere Length

One technique used to assess biological aging in the past has been to measure telomere length. Both Smith and I agree that epigenetic clocks are far superior for this purpose.

Telomeres are the sequences at the end of your DNA. Every time your cell undergoes a replication, you lose a little bit of that telomere, making it shorter and shorter over time. Eventually, you can start losing actual DNA. As the telomere shortens, the cell can start experiencing problems.

"Telomeres for many years have been thought of as the gold standard for aging because it's a process which highly correlates to how old someone is because

they're going to have more replications and more cellular turnover as they get older," Smith says.

However, in head-to-head comparisons, DNA methylation is significantly more correlated to the aging process than telomeres. More importantly, it's also more predictive of health outcomes.

"So, if we're really trying to predict the results, the disease and health span-related things which are associated with aging, DNA methylation is a much better way of doing that," Smith says. *"That said, telomere length is still one of those things that is a biomarker of aging. It is a separate process.*

If you were to make sure that the telomere length never decreased in a cell, you'd still see methylation-related biological aging. If you made sure that the methylation age was reset, you would still see telomere length aging. So, there's two separate processes.

In a recent review, they actually looked at twins and tried to ascribe how much of the difference in their aging process was affected by these different markers. They said right around 2% of the variance in phenotypic aging was due to telomere length, whereas right around 35% of that was based on these epigenetic methylation clocks.

So, while they both might be important, we definitely would think that the DNA methylation clocks are significantly better. But with that being said, we also can estimate your telomere length via DNA methylation and that's one of the reports that we do."

DNA Methylation and COVID Outcomes

During the course of the COVID pandemic, Smith has been collaborating with Cornell University's immunology department, looking at DNA methylation and COVID outcomes. They were in the fortunate situation of being able to compare pre-COVID measurements

with post-COVID measurements from patients who were getting routinely tested before the pandemic broke out, and then went on to develop COVID-19.

"We saw some really interesting things as it related to COVID-19 and aging," Smith says. The first thing they noticed was telomere length shortening. Several studies have now demonstrated that telomere length decreases with COVID exposure.

"I can't really speculate on the mechanism for that yet, but we definitely know that several studies with different measurements of telomere length have all concluded the same thing," Smith says. However, they also found a curious difference in biological aging as it related to chronological age. He explains:

> *"In our cohort, which is still relatively small, only 22 people, we saw that people who were over 50 tended to have advanced ageing as a result of COVID-19 exposure, where they were aging even with mild and moderate disease. However, people under 50 had a different response. People under 50 actually showed an anti-aging effect, where they actually got a little bit younger."*

The Promise of Very Small Embryonic-Like Stem Cells

Among the more exciting antiaging therapies now available is very small embryonic-like stem cells (Vsels). Vsels are so small, they're easily transported through the lung capillary, so if you were to get an IV injection of them, they can spread to the rest of your body without being broken down or distorted.

Now, your body has mechanisms to replenish Vsels. It's one of the strategies your body uses to stay healthy. Vsels are extracted from your peripheral blood, unlike regular stem cells, assuming that they're autologous, which means they're from your own body. They're not taken from your bone marrow or your fat tissue, which are the two most common sources for stem cells.

> **“ With the Vsels and plasma exchange, we are seeing multiyear age reversals, even with just one or two**

> **procedures. We're not sure how long that lasts yet … but we are seeing — just after the procedure and over a course of a couple weeks — age reduction in a very significant way. ~ Ryan Smith”**

Importantly, Vsels are pluripotential, meaning they can differentiate into almost any tissue in your body, whereas mesenchymal stem cells don't have as much differentiation capacity. This, I believe, make Vsels an ideal antiaging therapy.

Other Antiaging Strategies Showing Great Promise

Senolytics are also showing promise. A senescent cell is an elderly or aging cell that has lost the ability to reproduce. It just hangs around, not reproducing and not being cleared out. As a result, it starts creating inflammatory byproducts.

Senolytics selectively identify these senescent cells and destroy them. That's what senolytic therapy means. "Seno" meaning it's the senescent cell and "lytic" means that lyses, i.e., destroys, it.

Another interesting technique is called plasma exchange apheresis. This arose from studies in which the vascular systems of old and young mice were interconnected so that the mice started sharing blood with each other. Curiously, the older mice experienced a rejuvenating effect, and the younger mice experienced more rapid aging.

This led researchers to theorize that there might be something in our blood that influences aging and phenotypical health process. One evolution of this hypothesis is taking your own plasma out of your body, filtering it, putting in one or more new ingredients and then reinfusing it.

Lifestyle Strategies Help Lower Your Biological Age

In closing, here's a list of low-risk strategies that can go a long way toward lowering your biological age:

- Vitamin D optimization — Ideally, you want to maintain a blood level of 60 ng/mL to 80 ng/mL. Smith cites an interventional trial in which overweight participants reduced their biological age by 1.8 years on average, taking just 4,000 IUs of oral vitamin D a day for 16 weeks
- Optimize your metabolic flexibility — Core strategies include time-restricted eating or intermittent fasting and eating a diet high in healthy fats and low in refined carbs to optimize your insulin sensitivity, and eating your last meal each day at least three hours before bed
- Getting regular exercise
- Stress management — According to Smith, people who meditate or engage in other stress reduction strategies on a regular basis, tend to age at a slower rate than those who don't
- Limiting consumption of unsaturated fats — Omega-6 linoleic acid (LA) is particularly harmful. It's highly susceptible to oxidation, causing oxidative stress, and can remain in your cells for up to a decade. So, you want to eliminate vegetable/seed oils.

  If you're eating a standard American diet, 20% to 25% of your caloric intake can be LA. I believe this is one of the primary culprits for the massive increase in degenerative diseases. Before the advent of processed food, the typical intake was around 2%

More Information

If you're interested in exploring DNA methylation testing for yourself, all of the tests are available for purchase direct to consumer. The TruAge Complete Collection will give you

the metrics discussed in this interview — everything from telomere length to immune cell subsets, your intrinsic age, your immune age, and your instantaneous rate of aging.