Using DNA Methylation to Determine Your Biological Age
A Special Interview With Ryan Smith
By Dr. Joseph Mercola

Dr. Joseph Mercola:

Welcome everyone. This is Dr. Mercola helping you take control of your health. Today we are going up in a little bit of a different tangent and exploring some of the biological impacts of this infection that has driven our society to a near mass hysteria and paranoia. So we're going to be talking with Ryan Smith, who is a really clever and well-educated person in the area of longevity testing. He's founded a company called TruAge, which is probably one of the best commercial testing systems out there to determine what your biological age, not – actually, I'm sorry, your biological age as opposed to your chronological age. So you could be like, my case, 67 and be biologically 47. It's done through a process called DNA methylation, which is – I'm going to, I could expand, but probably not as well as Ryan, because, yes, this his area of expertise. So I will let him diverge off onto it.

Dr. Joseph Mercola:

But it's a really useful tool because you need an objective barometer, some type of standard. Otherwise, you have no idea what you're doing. You think you could be doing a lot of great things for your health, like exercise and eating a right diet and doing circadian rhythm optimization, but unless you have some assay to determine the cumulative impact of all the variables that enter into your life, and many of them hidden, like toxins that you're exposed to, you have no idea what's going on. So it's really powerful and relatively recent technology. We didn't have this when I was in med school. This didn't exist. We didn't even understand epigenetic aging at all. The concept was not yet discovered. So it's really good that you get up to speed on this because I think it could be a powerful tool for those of you who are interested in advanced strategy. So with all that background, welcome and thank you for joining us today, Ryan.

Ryan Smith:

Yeah. Thanks so much, Dr. Mercola. I'm happy to be on and definitely excited to talk about aging.

Dr. Joseph Mercola:

Yeah. Let me just, I forgot one thing, where I first met you. It was just a few weeks ago at Dave Asprey's biohacking event in Orlando, which I've been to a number of times before, but this was the best because I got to drive there from my house instead of flying across the country to Los Angeles, so yeah. Then you had a booth there and we talked and I was just really impressed with your depth of knowledge. So I think probably the best way to start is to maybe give us a little bit of your history so people know how you got into this and what motivated you to pursue this.

Ryan Smith:

Yeah, absolutely. So I've got a relatively strange background in the fact that I was a biochemistry undergrad. I went to medical school at the University of Kentucky, but passed my USMLE Step

1, but got to some of those clinical portions of year three and four and just absolutely hated it. So what I decided to do was make probably a very poor financial decision, but dropped out and really, at that point, created a compounding pharmacy called Tailor Made Compounding. So that-

Dr. Joseph Mercola:

Third year student or fourth year student?

Ryan Smith:

I was third. Yeah. Third.

Dr. Joseph Mercola:

Oh, wow.

Ryan Smith:

Yeah.

Dr. Joseph Mercola:

Well, that may not have been a bad financial decision, it may have been a really, really good one because you would've essentially been deep into debt and been a servant. Then probably with your commitment to integrity, would've recognized this fraud that's being passed as a pandemic and they probably would've taken your license away.

Ryan Smith:

Yeah. If I had known this world of integrative, functional preventative medicine existed in any reasonable way, I think I probably would've continued, but at the moment I didn't. So again, decided to cut my losses a little bit and then ended up creating a compounding pharmacy that really specialized in peptides and proteins and really new and innovative molecules. So we just hit a niche with that company and grew really, really rapidly. We were the fourth fastest-growing company in health care, really helping a lot of these integrative, functional physicians find products to really hit unmet needs in their patients. So that was a really, really exciting realm. Over the course of that time, it was definitely a learning experience in all things functional.

Ryan Smith:

But one of the things we always kept coming to is that a lot of the molecules and products we were using were still very, very new. So we wanted to have a way to objectively gauge how they were working. Particularly with a lot of these physicians working in anti-aging or longevity-based medicine, we really wanted an objective tool to gauge how these things were affecting lifespan and health span. So that search has been going on for a long, long time. Really, even in 1920s, they were taking someone's biological age or the age of their body by just taking their chronological age and adding one year for every pack per day you smoked or something of that – really crude measurements. But as you mentioned, this technology really took a massive step forward really starting in 2013 and, really, towards 2018, '19, it started to be used for the first time in clinical practice.

Ryan Smith:

So the moment the first interventional trial was published, looking at ways to reverse epigenetic aging, I knew that this is something I absolutely wanted to get into as a way to validate the effects that a lot of these therapies are having in an objective format so you can compare one thing to the other in really measurable and reproducible ways. So that's when we created TruDiagnostic. We created it really in March of 2020 right as the pandemic hit, but then started doing our first commercial test right around July of 2020. In that time we've – since that time, I should say, we've done a lot of interesting things with the company.

Ryan Smith:

We have over 30 clinical trials ongoing, looking at a variety of interventions, looking at, obviously, some things like the longitudinal effects of COVID-19 as well. Then we've also built out new algorithms, new ways to read these DNA methylation markers that we measure for other functional health benefits. I know one of the things you just mentioned as well was things like a history of exposures or the things you've been exposed to. DNA methylation is a really, really robust platform. But it's also very, very new. But 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.

Ryan Smith:

So this epigenetic platform, if there's one thing to take away from this talk, I think that it is 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. So I'm very excited about the field, but particularly the thing that we focus on at the company is aging, how to quantify that process, and then hopefully how to reverse it so that we can have really, really good results on increasing people's health span and lifespan, making them not only live longer, but live a quality life as well.

Dr. Joseph Mercola:

Yeah. I didn't realize you had started so recently because I believe I had my first test with your company within probably weeks of your company opening up. I didn't realize it was a new company. Because I was getting an intervention that we may talk about – well, VSELs, very small embryonic-like stem cells, which is probably the, I think we both agree, the best stem cell intervention out there, at least from the data that you have compiled. But before we go diving down that rabbit hole, I was wondering if you could step back a bit and just talk about the DNA methylation and the science. You mentioned the timing of it and it's only been around for a few years, but just precisely describe what that is so people can understand that. I mean, they may have heard the term, but they not really realized or understand what's going on. Corollary to that question was, was it Steven Horvath, Ph.D., that started this whole process or were there other researchers other than him?

Ryan Smith:

Yeah. So just give a little bit of history of this platform. This idea of epigenetic methylation really starts with one idea, which is that every cell in your body has the exact same DNA, right? If you were to test your eyes or your skin cells, they'd all have that same DNA, but they

obviously behave very differently, right? Your skin cells are obviously expressing a lot of genes that are different from your heart cells for instance. The way that they change that expression, what genes are turned on or turned off is via this process of epigenetic regulation. So it is a way to tell your genes, out of all the different things that you can do on your DNA, which ones should you actually be doing. So whenever these cells start and then they start to commit to different lineages, as they differentiate into different types of tissues, they change their epigenetic expression to regulate what genes are turned on and turned off.

Ryan Smith:

So I oftentimes liken it to a little bit like 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 and all that kind of thing, but if you don't know if it's on or off, then you're missing a big point of why that was created. It's the same with our cells. So 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 in large scale.

Ryan Smith:

So what we measure is DNA methylation, and this is the silencing of gene transcription, so when you're at the beginning of all your genes where they have those promoter sites, which we measure methylation at those locations, which then is associated with essentially decreased expression of that 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. So we measure specifically just that negative regulatory process, the DNA methylation.

Ryan Smith:

One other thing I should note is for anyone who's been in this integrative health space, they're probably familiar with this idea of methylation and MTHFR (methylenetetrahydrofolate reductase) and COMT (Catechol-O-methyltransferase) pathways and things of that nature. This is very different than that. We're not necessarily measuring your ability to methylate. What we're measuring is what the expression is on your DNA. As a result, the way that I would tell everyone to think about this is that this will be almost as big, if not bigger, than things like genetic testing or 23andMe-type platforms because instead of just investigating it once in your life, you can investigate it multiple times because these things are changeable. Your regulation of your DNA methylation changes over time.

Ryan Smith:

So we can really, due to some advances with big data analysis and artificial intelligence, what we're able to do is actually 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. We can correlate it to, for instance, if we wanted to predict athletic performance, we could predict athletic performance. So the idea, I think, is that right now this platform is absolutely in its infancy, but can be really trained to predict a lot of things if you have the covariate data in large scale.

Ryan Smith:

However, aging, particularly aging, was one of the first things to be looked at in this platform because it had such a high correlation. Whenever they first started looking at this, which started with publications in right around 2009, they found that DNA methylation was very, very highly related to age in a way that that was correlated very significantly. So, as you mentioned, in 2013, Dr. Steven Horvath at UCLA (University of California, Los Angeles) took the ball and pushed it a little bit further where he created a chronological age-trained methylation clock, which, with just a couple nanograms of DNA, could tell you how old chronologically an individual was with their DNA and it was very, very highly accurate. In fact, it was so accurate, I think it'll probably end up being considered for a Nobel Prize because it elucidated this idea that aging, this 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.

Ryan Smith:

For everyone out there who's new to this aging idea, it's important to note that aging is the number one 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 cancer or Parkinson's or Alzheimer's or most of these age-related diseases, it is to essentially not age. 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, but this molecular measurement can give us a much better idea of how we're aging. If we can treat this as a primary outcome, if we can treat aging, then we can reduce the risk of a lot of other chronic disease.

Ryan Smith:

The one statistic I always like to mention when I introduce people to this topic, it is that if everyone in the world were to be seven years younger biologically than chronologically, so if someone was 50 chronologically and had a biological age of 43, if everyone in the world had that same delta, we would have 50% less people sick. Overnight we would reduce disease by half. That is incredibly powerful statistic, which I hopefully can illustrate to people just how important aging is.

Dr. Joseph Mercola:

So I believe you told me previously that you're actually working with Dr. Horvath. He is a researcher. He developed the science, some of the initial science, but he obviously doesn't have a commercial application of that. So first of all, is that true? Then can you – well, let's address that. Then I have some other questions to follow up with.

Ryan Smith:

Definitely. So Dr. Horvath does not have a commercial application. He works through The Clock Foundation, which is a nonprofit that encourages collaboration on looking at the ways and reasons we age, but also then the treatments for this as well. Recently, Dr. Horvath has gone a little bit more, I would say. Research-based where he's doing a lot of mammal and mouse-based clocks. But with that being said, there are many people in the industry who have taken and up the

mantle of its application in the clinical space. So we hopefully, definitely are one of those to hopefully lead this process, working with a lot of great researchers.

Ryan Smith:

A lot of great work is being done at Yale with some of these really, really precise clocks. Really great work is being done at Dartmouth. Really, all these different areas have, I would say, specialties where we can look at things like the immune system, where we can look at different markers of aging. So right now, aging clocks are just exploding. There's more creative, more analyses of these marks every single day. So we're doing a lot of large-scale research projects to create the best clocks in class so we can really tell you all the processes that are happening within your body as it relates to the aging process.

Dr. Joseph Mercola:

Yeah. Thanks for that update because some of the people watching this already probably are aware of, have ever heard of the epigenetic aging clocks and the test for it, but what they probably haven't is have access to someone like you who is really leading in the field. So I'm wondering if you could share with us the current or the newest innovations that are out there in collaborations as you're in the process of developing. Is part of that also integrating other assays other than the methylation? Like you mentioned acetylation, which is the turning on of the gene. So is there an attempt to integrate both of those processes to get a more refined analysis of what's going on?

Ryan Smith:

Absolutely. I think that the idea here now is that, as I mentioned, this is where genetics was 30 years ago, but there's one big difference from between then and now, which is that we have ways of really interrogating this data with artificial intelligence and with data science procedures to really get useful information out of it. So there are a lot of different groups which are doing really great work.

Ryan Smith:

One that I love to draw emphasis to is Duke University with Terrie Moffitt, Ph.D.'s lab. They're doing actually some really fun work on these clocks, which don't tell your overall age, but tell you instantaneously how quickly you're aging. So what is your pace of aging right at this moment. I'm really excited about that one because it's incredibly accurate, but it's also a snapshot in time that's not influenced by some previous behaviors. I think we all probably have behaviors or things we've done in the past which we wish we wouldn't have, which might have impacted our overall biological age. This is able to tell you instantaneously how that process is going. So they're definitely leading with phenotypic measures of that clock.

Ryan Smith:

As I mentioned, the work at Dartmouth is able to do some really cool things with immune cell subsets. So just by taking one sample of DNA, they can actually tell you how many of which type of immune cells you have. So how many CD4 versus CD8 T cells. That's incredibly important as we create more accurate clocks and also get an idea of how our immune system is functioning. In addition to that, the work at Yale that's being done is taking a lot of the work

done by Dr. Horvath's lab with some algorithms that people might be familiar with, like GrimAge and PhenoAge, but making them much more accurate. So we can say that there's hardly any variation and some of the principal component clocks they've released now can reduce the sample size needed for some of these clinical trials by 1/20th, a massive amount, to make these results a lot more accurate and a lot more accurate on the interpersonal basis as well so that whenever you measure and then retest, you know that the signal you're picking up is actually aging signal instead of just noise as a result of maybe the fluctuation in the measurement of DNA methylation.

Ryan Smith:

So I would say that hose three locations are some of the most exciting for aging, but they're even doing some things now with senolytic clocks, which is probably something we'll talk about as it relates to COVID, where they can tell you the overall burden of senescence in your body and who might benefit the best from senolytic procedures like dasatinib and quercetin or fisetin, for instance. So this field of epigenetics is just beginning. Even outside of aging, there's now products in the market which are able to diagnose up to 50 types of cancer from a single blood test and actually tell you where it's at. So there are even algorithms which can predict schizophrenia or which can predict a variety of different things such as are you going to lose weight with caloric restriction. So this dataset is just being generated, but the applications and the reporting you can get from it are limitless. But in the areas of aging specifically, I would say some of the senolytic work, some of the work at Duke, Yale, are all very, very exciting areas.

Dr. Joseph Mercola:

Excellent. All right. So with that as a background, I guess we could start to delve into some of the – well, before we start some of the practical applications or the indications for the use of this as an assay to determine what's going on, are there other – you mentioned or alluded to the fact there are other companies starting to do this. How do you compare your company to some of the other companies in this space that are offering epigenetic clock aging, or assays?

Ryan Smith:

It's a great question and one that I always like to answer because this is such a new topic that there's not a lot of, I would say, education out there on what makes the best clocks or what makes the best analysis or measurement. There's usually two things that I like to draw attention to whenever I get asked that question. The first is the breadth of the measurement. As I mentioned, with new clocks and new analysis 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 or more insightful.

Ryan Smith:

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, very small amount of the total amount, but it's still significantly more than any of our competitors, which might be measuring at most 100,000. So we definitely like to scale because this is going to be a forward compatible platform. Much like DNA we're still – 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.

Ryan Smith:

So even in our company, 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. Again, it's only updated reports on a point in time. I want to make sure that that's clear because it's just at the time that you're taking that blood sample, but, again, information that we can gather from that can continue to be expanded for a long time. We use that, the sort of what is the basis of clinical literature, we use the same method that most researchers do so that as researchers come out with new information, we can report it.

Ryan Smith:

The next part of it, as I mentioned, is that 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, right? You could probably go to a fortune teller and they could tell you how long you'll live or how old your body is, but how do you know it's accurate? We really feel like publication is one of the main ways to have that scientifically valid and reliable measurement.

Ryan Smith:

Then the last thing that I always like to say is that the important thing when you're taking these DNA methylation samples is also 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. So if we were to measure your brain with the same algorithm we measured on your blood, we would get much, much lower ages than we would on your blood. If we tested your breast tissue, for instance, we get much, much higher ages than if we tested your blood. So the tissue type is very, very important, which is why we only use blood. Although it's not as easy to collect, it is definitely more scientifically reliable.

Ryan Smith:

So I would say that 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 that 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 which has been validated in the literature as well, which mainly at this point is either blood or skin.

Dr. Joseph Mercola:

Okay. So another aspect of testing, of course, is reproducibility. I'm wondering if you could comment on that with respect to the assays that you're using so that if you were to send in the same sample drawn literally minutes apart, would you get the same results?

Ryan Smith:

Yeah, absolutely. That's actually one of the biggest drawbacks of where epigenetic methylation aging algorithms have been. So that's always been a little bit of an issue. Even some of the newest algorithms out there had a mean absolute error of around 1.9 years, which can be highly, highly misleading. As you take one sample and then maybe six months later do another, a lot of that, as I mentioned, might be noise and not the actual effective aging on your system.

Ryan Smith:

So that's why I think some of the work from Yale, which has been happening from Dr. Morgan Levine's lab and particularly led by one of her postdocs, Dr. Albert Higgins-Chen, have been very, very exciting. They've used a statistical method called the principal component analysis to make these things very, very reproducible. So one of the metrics we use to talk about reproducibility is a measurement called the intraclass correlation, which is essentially, if you take two of that exact same sample, test it twice, how correlated are those to one another. Previously, as I mentioned, we've had some issues with that where the ICC values have only been right around 0.6 to 0.75, but now with these new algorithms, they're all above 0.95, which is incredibly reproducible and considered exceptional in the scientific community. So those algorithms that have been, I would say, are about to be published here very shortly with Yale are a big game-changer in the reproducibility of these metrics.

Dr. Joseph Mercola:

So it's really the algorithm that you're using that contributes mostly to the reproducibility of the test?

Ryan Smith:

Absolutely. Also, the size. I would also say the original algorithms like GrimAge and PhenoAge didn't use very many CPGs (clinical practice guidelines) whereas now these principal component analysis algorithms are using over 86,000. So being able to get a larger amount of data can definitely help improve the clocks. As we go forward, there are always going to be ways to improve these clocks as we get closer to isolating that real function of age and how age is playing into the acceleration of all these diseases. So these things need to be, I would say, changeable and modifiable as the data grows, which it's growing at an exponential rate.

Dr. Joseph Mercola:

Yeah. You had mentioned you're continuously modifying your reports just about on a monthly basis. I'm assuming that is the explanation or the interpretation of the data that you've compiled with respect to what it means for that specific individual. I'm guessing that's because the DNA methylation patterns, which would suggest turning off certain genes, either off or on, which you can demonstrate would correlate with specific diseases or at least risk for certain diseases. Is that the case?

Ryan Smith:

Absolutely. Even to give you a good example, even last week, toward the end of the week, there was a study published looking at how c-reactive protein versus DNA methylation measurements of c-reactive protein related to brain aging, and this inflammation and how it related to the aging

process. So one of the next reports we'll have will actually use that data to tell people what we might think their c-reactive of protein is as a result of epigenetic methylation and that is a better measurement of brain aging. So as this new data comes out, we have the data to interpret it. So 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.

Dr. Joseph Mercola:

Yeah. Good. So one final question before we delve into the more exciting and, I think, clinical applications would be a comparison to another effort to assess biological aging, which is telomere length. Maybe you can just describe briefly what telomeres are and why you and I both believe that epigenetic clocks are far superior.

Ryan Smith:

Absolutely. So for anyone who's not familiar, telomeres are the end caps of your DNA. They're the sequences at the end of your DNA, which over time are slowly shortened. Every time our cell undergoes a replication, we lose a bit of that cap on our DNA. When this keeps happening, as we get really a lot older, those can get actually too short and start to – we can actually start to lose DNA, which is important to us. So when that process happens, we can have the cell essentially have some problems. So telomeres for many, many years have been thought of as one of the best gold standards 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.

Ryan Smith:

Unfortunately though, telomeres in several biological reviews, and I would say don't take my word on this, but in these 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. Just to give you an idea, the R-value between age and telomere length, it fluctuates right around 0.3 whereas the R-value for some of these DNA clocks with age is sometimes over 0.9. So there is a significantly higher correlation. It's better at predicting health outcomes.

Ryan Smith:

But with that being 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 actually still see telomere length aging. So there's two separate processes.

Ryan Smith:

But 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 just to give you a relative idea of

scale, 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 actually can estimate your telomere length via just DNA methylation and that's one of the reports that we do.

Dr. Joseph Mercola:

Excellent. Well, thanks for that great answer. Let me just interject a definition or at least an explanation of something you mentioned I think many people who haven't studied science wouldn't be aware of, and that's the R-value. You quoted a number of 0.3 correlation with the telomeres versus 0.9 with the DNA methylation. That R-value can go anywhere from 0 to 1, 0 being absolutely no correlation and 1 being 100% correlation. I think you can see at a 0.3, it's pretty poor versus 0.9, which is pretty close to being perfect. But that was a perfect segue into the next portion we'd like to discuss, which is the clinical applications. So I think we should start with the hottest topic out there, which is the recent work you've done showing the correlations with the DNA methylation and the outcomes in COVID. So if you can jump in there, that'd be great.

Ryan Smith:

Yeah, definitely. So we've been working as our collaborator on this project with Cornell University and their immunology department. One of the interesting things about our patient population is that a lot of them are retesting, so we were able to get a good idea of the baseline for these patients. Then whenever they developed COVID, we were also able to see the changes when they retested. So that data set is one of the ones that we were lucky enough to have at a very early stage in this investigation. In that analysis where we actually used those new algorithms from Yale, those PC, the principal component algorithms, we saw some really, really interesting things as it related to COVID-19 and aging.

Ryan Smith:

The first thing we saw, which is, I would say, has been described relatively robustly in the literature now is that we saw telomere length shortening. So I think that that has now been shown in several different studies where telomere length decreases with COVID exposure. I can't really speculate on the mechanism for that yet, but we definitely know that now several studies with different measurements of telomere length have all concluded the same thing. So that was one of the interesting things we found.

Ryan Smith:

However, one of the other interesting things that we found was the difference in aging as it related to age. So in our cohort, which is still relatively small, only right around 22 people, we saw that people who were over 50 tended to have advanced ages as a result of COVID-19 exposure where they were aging even with mild and moderate disease. However, one of the interesting things that we also saw is that people under 50 had a different response. People under 50 actually showed an anti-aging effect where they actually got a little bit younger. So there were a lot of reasons we might postulate that change, but we did see a relatively clear line of demarcation.

Dr. Joseph Mercola:

Interesting. I would have speculated hormesis would be one of them, but you have enough resiliency and reserve capacity to actually use that to activate your biological mechanisms, to counteract that, which in result decreases your aging response, whereas that resiliency disappears or is radically diminished when you're over 50.

Ryan Smith:

Absolutely. That was actually our speculation on it as well, which is that – particularly having to do with some of those naive T-cell response where maybe people under 50 don't have the necessary T-cell response to mount that hormetic response while people under 50 definitely do. That's why we're actually seeing that anti-aging effect in younger individuals or no aging effect, but seeing an aging effect in people who are unable to mount that response. So that is definitely our hypothesis, but we, with that being said, are trying now to investigate other similar types of infections to see if we see something similar to that with that age demarcation as well. So that was definitely an interesting finding.

Dr. Joseph Mercola:

Yeah. So I'm particularly intrigued with the concept of T reversal or growth, because there's certainly been a lot of research into the effort to attempt to lengthen telomeres with supplements. I'm wondering if some of the interventions that you're measuring, other than supplements to lengthen telomeres, where you've seen the significant reduction in biological age, if those interventions have also addressed telomere length?

Ryan Smith:

So at the moment, I would say that, and it's important. I also want to make sure everyone knows that this idea of DNA methylation and these interventional studies where we're looking at befores and afters is still very, very new. The first ever interventional trial came out in September of 2019, right before the beginning of the pandemic. Obviously, that slowed a lot of research. So we don't have thousands of studies or even hundreds of studies to look at. We're really working with 10 to 15 at the moment to look at some of these effects.

Ryan Smith:

But I can say that we if we see some anti-aging effects, we don't always see telomere elongation effects. Again, they tend to be separate processes. With that being said, these telomere algorithms via epigenetic methylation, so we're not actually measuring those telomeres, we're just measuring methylation and using it to predict telomere length, which tends to be fairly accurate. So I should also note that even though we're not measuring it directly, it's still very, very new. So a lot of those telomere analyses have not done on even some of those other published studies. So right now we don't see that telomere length is correlated to reductions in biological aging or vice versa.

Dr. Joseph Mercola:

Okay. Thank you for that refinement of understanding the telomere association. So how about some of the other clinical conditions that you've noticed and that we could talk about some of the interventions that you've been impressed with, with respect to being effective at reducing biological aging?

Ryan Smith:

Absolutely. One of the things I think it's important to talk about is a little bit about the baseline of just us, generally. Most people, depending on the algorithms you use, in the United States tend to have relatively advanced aging. One of the other things is that men are usually much more likely to have advanced aging than women. So that might make sense to most people, as we know that generally women tend to live longer, but with that being said, I would say that those are important baseline characteristics. However, some of the most exciting therapies that we've seen to work are definitely things that we've briefly mentioned here before, some stem cell procedures, particularly those very small embryonic-like stem cells. We've seen plasma exchange or this plasma apheresis process, which has a really interesting history, also have some very good results.

Ryan Smith:

Then we are actually about to publish another trial, which is very exciting where we use the senolytics that we mentioned earlier, dasatinib and quercetin, over the course of six months and saw multiple age reductions. So those are some of the newest and most exciting things that I would put on the list, but the data which has already been published has shown things like combinations of metformin, growth hormone and DHEA (dehydroepiandrosterone) as ways to reverse this epigenetic aging process, supplementation with some methyl-related factors if you have some deficiencies there, and then vitamin D being one of the, I would say, really robustly studied ones, which shows multiyear age reductions and tends to work better in individuals who are relatively overweight. Then with that, we know a lot about diet and lifestyle and how to change these things as well.

Dr. Joseph Mercola:

Yeah. Yeah. But so the three most effective interventions probably correlate with what my understanding of the best therapies or strategies are. One would be VSELs as the optimum form of stem cell intervention. There's a wide variety of people who are getting stem cells. Let me just expand a bit on it right now. Again, it's VSELs is short for very small embryonic-like stem cells. You would think it'd be V-C-E-L-S, but it's V-S-E-L-S. The S is short for small. They're so small, they're about 40 nanometers, that they easily get transported through the lung capillaries so that if you were to get an IV injection of them, it can spread to the rest of your body without being broken down or distorted. So that's a beautiful component of it.

Dr. Joseph Mercola:

Secondly, is that they tend to be in everyone. So they don't disappear with age. Your body has some mechanism to replenish these. It's one of the strategies your body uses to stay healthy. They're extracted from 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. Then they're not taken from other humans. They're like mesenchymal stem cells. I think one of the most important components of it is that they are pluripotential. Now, what the heck does that mean? It means that they can differentiate into almost any tissue in your body whereas some of the mesenchymal stem cells are – it's not pluripotential. It's totipotential I think. So they don't have as much differentiation capacity. So that, really, it is the ultimate type of stem cells if you're going to use it.

Dr. Joseph Mercola:

I'm a very strong proponent of that. It's not really widely available now, but will be, because there's some legal issues that are having to be worked through, but it will be probably in 2022 most likely. At that point, I couldn't recommend them more heartily. Essentially it's very similar, maybe people might have heard of PRP, which is short for platelet-rich plasma. It's a similar process that these cells are isolated from peripheral blood that's drawn from just a regular venipuncture, and then they're spun down and with the VSELs, well, with PRP, there's no type of processing other than isolation of the cells before they're injected back into the tissue or into the blood. But with the VSELs, they're actually activated with the laser, which reawakens the cells and allows them to be activated so that they can respond to the environment that they're placed into and reproduce into the appropriate tissue. So that is the best form of VSELs.

Dr. Joseph Mercola:

But then we've also got the senolytic – so you got the VSELs. I just started for the expansion on that, but it's a topic that most anyone not heard of, then you've got the plasmapheresis, which you could probably go into some depth on this, and then we got the senolytic therapy. So the senolytic therapy is an intervention that you just mentioned earlier. There's a number of nutrients or drugs like quercetin and fisetin and dasatinib, which is a drug that can then remove these senescent cells.

Dr. Joseph Mercola:

What is a senescent cell? Senescent cell is one that is essentially senescent. It's an elderly cell, aging cell, that is lost the ability to reproduce. It just hangs around, not dying, not getting cleared out, and creating these inflammatory byproducts that not only mess up that cell itself, but leak out the cell and really damage severely. Kind of like a rotten apple in a basket of apples. It just damages everything around it. So there's these interventions can go in 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 it or destroys it.

Dr. Joseph Mercola:

So of those three, have you – and if you can maybe talk a little bit more about plasmapheresis because you have a better understanding than I do, and if you could just rank them and from what you've seen of the limited, and I completely understand this is relatively new knowledge and you're still in the process of compiling the data, but from what you've compiled so far, how would you – curious as to your ranking of them?

Ryan Smith:

Yeah, definitely. So just before I rank them, I definitely want to give a little bit of background on the plasma exchange apheresis. Just because especially, I think, that background is particularly interesting. Because what they did to first uncover this was they actually took young mice and old mice and actually put their vascular systems together so that the young mouse was actually giving their blood to the old mouse and vice versa. What they actually saw was that the young mouse actually had a rejuvenation, or I should say-

Dr. Joseph Mercola:

Yeah, [crosstalk 00:41:33]-

Ryan Smith:

-the old mouse had a rejuvenation effect where the old mouse got younger and more healthy. Then surprisingly, a little bit vice versa, they also saw that the young mouse actually got older and actually had worsening of some of those physiological symptoms. So what they started to think of was, "Hey, there's probably something in the blood that is causing this aging or poorer phenotypical health process." So that what began its investigation into what markers in young blood versus adult blood are different and how can we, maybe, influence this type of process.

Ryan Smith:

Without going too much into it, one of the evolutions of that was this idea of taking someone's own plasma, taking it out of their body, filtering it, putting in a few other ingredients and then re-infusing it almost as a way to decrease some of those unfortunate or maybe those pro-aging different molecules or signaling molecules. So with that, some of the data on that has been done with things like the AMBAR (Alzheimer Management by Albumin Replacement) trial, where they've looked at Alzheimer's and using this as a therapy to prevent cognitive dysfunction with age. They've got really, really great results.

Ryan Smith:

But we've also, I would say, in both mouse models, actually via some of the work with Dr. Horvath and in some of the clinical trials that we're actually running now, are seeing to aging effects of just that plasma exchange process. One of the things that, that we really try and look at as we look at these therapies is multiyear intervention changes where with one intervention we can see multiple years reduced. The reason is we want everyone to get to that seven-year delta, right? To be seven years younger where they're experiencing then 50% less likely cause of all these diseases. So the plasma exchange is definitely an exciting therapy. Again, not really widely available just yet, but definitely is exciting for the future.

Ryan Smith:

So ranking these is, as you mentioned, very difficult because we're not always comparing the same dataset, the same in patient subsets, et cetera. But right now, I would say that all the dasatinib and quercetin looks very, very reliable, especially in older individuals at age reduction. It doesn't have those same multiyear age reductions that we're seeing.

Dr. Joseph Mercola:

Interesting. Interesting.

Ryan Smith:

So it does look to be positive and reliably positive. It doesn't have some of those multiyear age reversals and as big of a gap as we're seeing with maybe VSELs or plasma exchange. I would say with the VSELs and plasma exchange, we are seeing some of those multiyear age reversals, even just with one or two procedures. We're not sure how long that lasts yet. We're not sure if they're two months later or a month later that it might reverse, but we are seeing just after procedure and over a course of a couple weeks that we're seeing age reduction in a very, very

significant way. So I would say that between those three, which are the most exciting, I think that I would put the VSELs so far as well as the plasma exchange at the top and then at a relatively far second, the senolytics. Although, again, I think that any of these age treatment protocols are better off with multifaceted multi-targeted pathways. So I think that the combination is also something that can be very exciting.

Dr. Joseph Mercola:

My goal is to get a 40-year reduction since I have access to these therapies and be one of the people that lower it most effectively. But I'm curious, do you think it's possible then in plasmapheresis that you are actually removing senescent cells and maybe that's why it's so effective?

Ryan Smith:

Unfortunately, I wish I would knew more about the actual physical process. It's something that I'm not generally, I would say, as up-to-date on. I think that one of the leading candidates and one of the studies I'm very excited to do is looking at the proteins that might be changing, particularly in that plasma. Because the plasma is very rich with protein material and in terms of epigenetics, it has a lot of cell-free DNA, which is generally DNA from throughout the body. So I think that maybe the leading idea is that it might be filtering out some proteins, which might cause this anti-aging process. One of the things they also infuse is albumin, which binds to a lot of proteins. So I think that this replacement of albumin or the updated filtering out some of these abnormal proteins might be the reason it's having such an effect.

Ryan Smith:

I also think that it's important to mention that the thing that's been studied the most for which is cognitive dementia in Alzheimer's is also known to have abnormal protein development, right? With those beta and tau amyloid plaques in the brain. So I would, without being an expert in this, and I would definitely refer to others like the Conboys from Berkeley or a couple others, I would generally say that I would anticipate that's the mechanism, but not sure right now. All I know is that from the data we're seeing, it's highly effective in reversing these clocks.

Dr. Joseph Mercola:

So is there anyone that's been looking at actually the proteins that are filtered out?

Ryan Smith:

I should say it's starting to happen, particularly with the advent of a new type of technology where they're able to not just look at certain proteins, but look at un-targeted proteins. So they can just say, "We're going to look at all these different factors." It's the Seer bioinformatic platform. They're able to then capture even really, really small scale proteins to look at that. So the research is just now beginning as, again, some of these other of methods are just being now created.

Dr. Joseph Mercola:

Wow. Wow. Just curious as to your thoughts are with respect to the ultimate reduction in biological age. Do you think there's some plateau and do you think it would be an absolute value

with respect to a number of years or more likely linked to a percentage of the reduction? So maybe 50%.

Ryan Smith:

Yeah. The early evidence that we've seen in our patients is that it's probably going to be more of a percentage because some people have, even genetically, are predispositioned to have worse epigenetic ages. So I think there's probably some factors which are unfortunately immutable, which might then be reflected in that percentage rather than the absolute. But some really exciting work is being done here. One of the things that people are really excited about is this idea of cellular reprogramming.

Ryan Smith:

This has gotten a lot of news recently because of a company in the anti-aging space which was just created by Jeff Bezos and is really well-funded. Actually, I think Dr. Horvath is actually going to be going to this company called Altos Labs to work on some of this cellular reprogramming where there's actually a step in embryo genesis, right? Whenever we're creating a new human where the epigenetic clocks are reset completely. They're set to stage zero. So there are a lot of people who believe that with certain type of things, particularly one thing called the Yamanaka factor, which is a combination of, obviously, proteins can reset that epigenetic clock.

Ryan Smith:

One of the most notable, I would say, experiences in that work or publications at work was been from Dr. David Sinclair's lab in Harvard where they used these Yamanaka factors to actually reprogram the epigenetic age of eyes in these mice. In these mice, when they did that, they were able to actually restore age-related vision loss. So I think that with the therapies that we're working with now, there's probably going to be a plateau and a plateau that is still, I would say, a proportional or a percentage-related factor. But I think that in the future, if the cellular reprogramming works out, I think it could be very, very exciting. It's just a matter of when it will actually be commercialized as it's a much more riskier strategy.

Dr. Joseph Mercola:

Yeah. I couldn't think of a better summary than you just gave because it – clearly, if you first hear about the Yamanaka factors, become really intrigued with it and the exciting potential, but when you start to go explore it in deeper details, is associated with a load of risk. I personally don't think it'll be really available in my lifetime because there's too many darn risk[s] with it. Primarily it's you have to have an adenovirus to integrate it into the cells and you have to target it. You have to turn it off, you have to turn it on.

Dr. Joseph Mercola:

In Sinclair's work, he uses a molecule called doxycycline, which is a tetracycline antibiotic, which is, I have no idea why they use it because it seems really foolish. I mean, tetracycline is not an innocuous drug. Why wouldn't they use something like a nutrient or something? But I guess maybe a nutrient would wouldn't work because you'd be exposed to it all the time. You wouldn't have as much control. So it'd have to be something foreign that your body doesn't normally – but there could be a lot less innocuous molecules they could have used. So I'm

excited about the potential like you, but I'm a bit more concerned about the toxic unintended side effects of this.

Ryan Smith:

I couldn't agree more. Yeah, no, I couldn't agree more. One of the other things that we're particularly highlighting are things that everyone can do because although we might be talking a lot about these more exotic type therapies, which have multiyear age reductions, there are things that everyone can do today to reverse their epigenetic age just through diet and lifestyle and nutrition and some of those other things. So I think that for anyone who's contemplating doing this testing or even working on their own aging process, I would say that don't be scared if you can't get some of these procedures because you can still have an impact and still make a very good impact over time.

Dr. Joseph Mercola:

Yeah. So why don't we just dive into that now? I can give you my concepts or beliefs of what I think would be some of the most powerful. That would be probably vitamin D optimization to 60 to 80 nanograms, optimized metabolic flexibility, so not be insulin-resistant, and usually the clinical side effect of that is being overweight if you are insulin-resistant, and then probably exercise, I think, would be my top three. So have you looked at these, I don't know if you do, when you get to send the sample in, I don't think you do an analysis of their lifestyle events, so you may not have been able to compile the data on that, but what are your comments on the most effective interventions?

Ryan Smith:

You're exactly right. I would say that one of the things that – although the interventional trials have been limited because it's so new, one of the interesting things is that we actually have a lot of epidemiological data because we can actually take samples which have been biobanked for the last 40, 50 years-

Dr. Joseph Mercola:

Oh, good point.

Ryan Smith:

-and then look at how these factors are affecting. So one of the things you mentioned, insulin resistance, or, I should say, insulin sensitivity, vice versa, insulin sensitivity is definitely a big factor there, as we know. So I would absolutely agree with that.

Ryan Smith:

I would also say, we actually do have one interventional trial on the vitamin D, which is that in just 16 weeks, over the course of 16 weeks, there was an average of right around 1.8 years of reduction from overweight individuals who were taking 4,000 IU per day of vitamin D. Again, whenever we're talking about multiyear age reductions, that's hard to do, 1.8. So again, those patients were definitely a particular subset. So I wouldn't say we see that change for everyone, but vitamin D definitely seems to be positive.

Ryan Smith:

With exercise – and exercise is actually a very interesting one. Actually a lot of the things that we see are very similar to what we see with exercise where some is great, but too much can actually be a negative thing where we see there's definitely a sweet spot. We think that's because, particularly in a lot of our professional athletes or Olympians who undergo a lot of physical activity, we probably see more increased reactive oxygen species, a worse ability to deal with all these constant insults, which are happening. So we actually see similar things with even drinking alcohol, for instance, where one to two drinks of beer or wine per week are actually associated with better ages whereas heavy drinking is associated with around 2.2, two years of negative age acceleration, or, I should say, age acceleration, which is a negative thing. So I think that there's a definitely a sweet spot.

Ryan Smith:

But the one lifestyle thing which surprised me, we consistently see again and again and again, is the impact of stress and stress management. I've never been a huge one for mindfulness or meditation because I always ask myself as I'm sitting there, "Am I doing this right? Am I accomplishing what I intended?" What we see now is that the people who do mindfulness, who do meditation, who have stress reduction strategies in their life, tend to age at a much slower rate. So that was one of the biggest and most surprising things for me as someone who's not always attributed too much of a medical, I would say, impact of stress. It is absolutely one of the things that we see move the needle in the biggest way.

Dr. Joseph Mercola:

Okay, good. I just wanted to comment on the vitamin D. I'm not surprised that they found that in that study you quoted. But my guess is that you really – this is so pervasive because I've been studying vitamin D for so many years, but almost – the vast majority of studies publishing vitamin D, they fail in their methods miserably because they fail to actually measure the blood level. My guess is they did that in the study that you quoted because they probably gave these overweight individuals 4,000 units of vitamin D. Well, it doesn't matter they give them 4,000 or 40,000. The key is that you have to move that vitamin D level to the 60 to 80 nanograms per milliliter sweet spot to activate optimized epigenetic regulation of the DNA to get the benefits.

Dr. Joseph Mercola:

It's the simple thing that people can do and it's really one of the most powerful interventions for health, is just to go out and get your blood tested. You don't have to get a doctor's order. You can get these tests online. It's a little bit painful, but you have to prick your finger and you put about, I don't know, 10, 12 drops of blood on these cardboard blotters, and you mail it in, and in a few weeks, you get your results. So simple to do and it's so, so powerful.

Dr. Joseph Mercola:

Then I think the other thing that may be on par with that, that we didn't discuss, but there's the Harman free radical theory of aging, which is subsequently being modified to the mitochondrial free radical theory of aging, I believe, is appropriate here because, really, it's all about oxidative stress and the generation of free radicals. The huge mistakes were made in applying this anti-aging is that people were taking massive amounts of antioxidants, which indiscriminately

suppressed these free radicals, some of which are highly beneficial. So you need to selectively target them.

Dr. Joseph Mercola:

But ultimately, the reason oxidative stress is such an issue is because you have these damaging molecules that are floating around the body, but if there's no target for them, and this is the key that I only understood just relatively recently, then they're not going to really be that dangerous. So what is the target? The target is unsaturated fatty acids, which get embedded into your biological tissue for years. Years. So when you eat sugar, yes, it's not good because it could lead to insulin resistance. We already said that's an issue. But you can change that insulin resistance in literally days or weeks. But to change the molecules that are highly susceptible to this oxidative stress would take years. Many years. Sometimes five to 10 years.

Dr. Joseph Mercola:

So the consequence of this is that to reduce the most dangerous form of fatty acid, which is an omega-6 fatty acid called linoleic acid, and it's pervasive in our diet. Historically, we've had like 1% to 2% of our total calorie intake with linoleic acid. Now it's 20% to 25%. There's little to no doubt in my mind, and I could be wrong, but I don't think so, that this is the one of the primary culprits for the massive increase in epidemics of degenerative diseases that we experienced, is linoleic acid input, which just gets embedded into cell membranes and are just predisposed to these free radicals that get generated and just sets off this oxidative cascade that damages all these tissues.

Dr. Joseph Mercola:

So, to me, vitamin D optimization and just eliminating almost all, all linoleic acid in your diet... Because if you're eating food, you're going to get enough. Essentially your body can't make it. But it's in virtually every food you eat. So the key is no seed oils, no vegetable oils, no chicken, no pork. Stay away from sauces in restaurants or salad dressings because it's all loaded with this garbage. I think that go a long way. I'd love to see some studies being published on this because I think that the results would be outstanding. Unfortunately, it would have to be long-term. It's not a singular intervention like VSELs. You'd have to do it for years before you'd see the results.

Ryan Smith:

Yeah, definitely. I should mention that a lot of the epigenetic researchers who were responsible for some of these clocks, one of the, I would say, big holes and gaps in this research has been comparing how lipidomics affect epigenetics. So that is a definitely an area that people have targeted as an area that they're going to look at in the future. So hopefully we'll be able to know a little bit more about that as well. But even from a dietary perspective, I think that the recommendations, those really pragmatic and clear recommendations, are similar to what we see in the literature where we see things like Mediterranean diets do very, very well with epigenetic age in multiple publications. So again, hopefully we'll have an answer here soon.

Dr. Joseph Mercola:

Yeah. Yeah. That's good. So I'm obviously really impressed with your knowledge base, your commitment, and the quality of the testing that you do. So if anyone's interested in exploring this

for themselves, perhaps establishing a baseline because it is good to have a baseline, normally it's going to – maybe you can comment on this, the rate change that you'd expect, at least what you've seen, outside of the interventions of VSEL and plasmapheresis, is relatively slow. But it is good to have a baseline because at some point you might have access to VSELs or plasmapheresis or some of these other things. Like maybe you haven't looked at DNA optimization. My guess is that many people, if we have a suboptimal vitamin D levels, they can get maybe a two, maybe even a three-year increase by changing a vitamin D level that's been chronically low, like 20 or 25 and get it up to 60. That's going to be a big difference in your life. So why don't you comment on those and then give us information on how someone could get this test done for themselves?

Ryan Smith:

Yeah, absolutely. This test is available direct to consumer. So consumers can go on our website at TruDiagnostic.com to order this. It's the TruAge Complete Collection, which it reports out on all of these different metrics, everything from telomere length to your immune cell subsets to your intrinsic age or your immune age. So we can report out on all those things, including your instantaneous rate of aging. Then if there's really one thing I would recommend optimizing to, it is probably that rate of aging because that changes a little bit more quickly than some of these other metrics. If you can make sure that stays lower over time, we know it directly relates to better health span, where we see less sarcopenia, more muscle mass. We see as this rate of aging increases, we also see cognitive decline and IQ loss changes. We see facial aging. So if you're really one to optimize, I'd definitely highly recommend that rate of aging as well.

Ryan Smith:

If you ever have any other questions or would like any more data, feel free to reach out to us at TruDiagnostic. Our contact information's on that website. Happy to always point you in the right direction of some research. If there's any researchers out there looking to see how maybe their product, or certain types of things, for instance, like linoleic acid, might affect aging, we'd be happy to collaborate. So feel free to reach out to us. We'd love to talk more.

Dr. Joseph Mercola:

Okay. What's the name of the site again? TruDiagnostics.com?

Ryan Smith:

Yeah. Yeah. T-R-U-diagnostic.com. And-

Dr. Joseph Mercola:

Diagnostic. Okay. Not plural. Diagnostic.

Ryan Smith:

Not plural. Correct.

Dr. Joseph Mercola:

Good. Yeah. Then all the information will be there. So it's a great tool. I'm probably going to be using it for many, many years. I'm so glad that we connected and you were able to share your insights on this. I believe it is a really important thing, especially the insights on the damage to aging. Not surprising and actually what I guess you would have predicted, if you were to make a guess, that COVID has on aging, so I was – but what was surprising is that it actually was potentially hormetically medically beneficial for younger people, unless you want the people who get the COVID "killshot" and die of myocarditis at the age of 15 or 18 years old.

Ryan Smith:

So yeah, no, definitely. Then as we come up with new studies, I mean, we're going to be publishing quite a bit now, coming out with, I think, some data on COVID, the senolytics, things like bariatric surgery, et cetera. So hopefully we'll be able to talk again and update everyone on some of the best ways to reverse that aging process.

Dr. Joseph Mercola:

All right. We'll look forward to a future update.

Ryan Smith:

All right. Thanks so much, Dr. Mercola.

Dr. Joseph Mercola:

All right. Thank you.