Introduction to Epigenetics and Biological Age

All right. So we've been talking a lot about genetics and the impact of genetics because that's what we do as a company, what we know and what we understand and what we can teach.

And in that, we've been sort of sprinkling in comments about epigenetics here and that we've been talking about the impact of, here's foundationally where you're at, but, you know, to understand your current spot in time that what's that measure of, you know, where I'm at today, what do I need to focus, what's broken?

Well, your epigenetics speaks to that and everything we've been speaking about epigenetics up until now has been more about the choices. Meaning what do I eat?

How do I exercise versus what do I measure? That's what's been missing for some time because the measure has been so complex. So who's joining us today?

Ryan Smith. He runs True Diagnostic, which a lot of you have already heard of or maybe even have tried the testing out to determine your biological age with very specific markers, what's going on on the inside and then exactly where to focus.

Ryan, thanks for joining us. Yeah, thanks so much for having me. Steve, I appreciate it. Yeah. This question always comes up. It's, you know, what is epigenetics?

Why epigenetics? Why not epigenetics? Why are you only telling about my DNA? But then the people asking don't even know what they're asking. So first of all, there's a very sort of base level understanding of what that even means.

And we speak to it to that level, you know, what do I eat? How do I exercise? But there's so much more because the tools weren't there. We don't speak about that so much more. But now the tools are there.

So tell us in a nutshell, what do people need to know about what their epigenetics can tell them? Yeah. So so I think it's important first to just define the process.

Right. And the way that I usually talk about it is by saying, you know, every single cell in your body has the same DNA, right? If you were to test your heart cells or your liver cells, you get the exact same DNA sequence.

However, those two cell types behave very, very differently, right? You know, you're obviously have a heart phenotype and a liver phenotype. And so, the question is how are they so different?

And really the way that we describe that is via epigenetics, what genes are sort of turned on and which genes are sort of turned off. And so that's sort of how we describe it as epi obviously means above the genome.

And so these are changes are happening above the genome to regulate gene expression. And so as you mentioned Kashif, this is a still a very, very new field.

This is you know, something that that is absolutely in its infancy really. You know, in 2010 this started with investigations of right around 50,000 locations of a genome.

You know, in 2014 15, it got a little bit more robust for 40, 50,000. Now we're able to look at 850 to 900,000. And that's out of 29 million spots per cell.

And so this is nowhere near the level of development that that genetics has had over the course of multiple

decades. But but it is starting to sort of be created where there's a robust data set where we can actually look at these markers and be able to tell certain things about your health or sort of, you know, even predict certain types of outcomes.

And so right now, epigenetics is definitely in its infancy, but one of the biggest areas where it's applicable is sort of in age related diagnostics. And being able to tell you the age of your body, that's really where it started.

But it will impact every area of medicine over the course of the next decade or two. So how variable is that when you say, like, you know, there's switches that get turned on or off or the epi above the DNA, the expression changes.

Is it like, static where, you know, there's things that cause a problem or is it a constant? I mean, your cells, there's several thousand functions going on in any given second in your cells.

So is it that level of variability. So it depends on the location. There's some some locations in your genome which are widely changed, others which almost never change.

And so it all depends on location. It also can generally depend on the cell type. And and that's another I would say benefit and limitation of these cells.

Right. Tissue type matters. You know, as our cells go from, you know, these pluripotent stem cells and they, they differentiate themselves into different cell types, the cell types that would, you know, turn into, you know, lymphoid tissue or turn into solid tissue or bone.

What they do is they turn genes off or turn genes on permanently.

How Epigenetics Works and Why It Matters

And so every cell type is different, which is actually one of the biggest limitations, in, in epigenetics as well, is because not only do we have to worry about, you know, the actual sequence and our accuracy of that diagnostic, we also have to worry what cells we're getting and how we control for those differences.

And and then again, as you mentioned, how fluctuating are those sequences? If if one sequence is taken in the morning and one sequence is taken at night and they're very different, then that can be, you know, pretty problematic to create any insightful information.

And so, you know, the benefit of epigenetics is that that there are temporal, right? You can see changes in real time, but that's also a big problem in getting really accurate research.

So there's the sort of in time variability. But then there's the permanent change. And do we do we know yet how that happens. Meaning that this is a hard sell.

It only accesses a certain piece of the genetic instruction manual so that it can operate as a hard sell. Do we understand that yet how that happens. Yeah.

So so we definitely are understanding more of that I would say. So. We know a lot. We know that, for instance, how these cells, commit to different structures.

We know the sort of enzyme and protein machinery which works to activate or deactivate genes. What we don't understand is maybe why certain genes are deactivated or activated in certain scenarios.

And generally we also don't know about how to read that. So even if we get that data, we don't know how to associate it with certain types of outcomes.

And so that's what's happening now. And that's why I try and say we try and do it through diagnostics is to create

the Rosetta Stone, so to speak, of how to interpret these methylation marks.

And in order to do that, you really, you know, need things that particularly need computer learning and artificial intelligence, which really hasn't been, I would say, where it needs to be.

And now we're finally getting to a place where, with enough data and with enough computer learning, we can really train these algorithms to predict a multitude of things.

I've already mentioned, you know, sort of aging, which is one of the things that we do as a primary, aspect. But even already there are blood tests which can take, you know, some of the plasma from your blood and tell you if you have over 50 different types of cancer, and also where that cancer is, you know, we can predict death fairly accurately.

And so it's sort of a new world of big data. But but you need to make sure you're doing those investigations in the right way with very clear and delineated outcomes.

And and so, again, right now, it's a little bit less actionable than your traditional genetics, right? I mean, it we just don't know enough definitively about some of these, these features. But we're starting to learn.

And aging is definitely, again, putting forward the majority of the research in that area. So you I mean, you know, when you, you built this business in this research company and your focus or the primary purpose for which clinicians work with you is around aging and this biological number, it's, you know, chronologically, you can put whatever you want based on your birth certificate, but what's going on in the inside?

So how did you get there? How did you determine that this is this is the most useful function. And how do you even determine what biological age is? Yeah, it's a good question.

You know, this is, I wish I could say I could take the credit for this, but, you know, I think that the majority of this, this research was really spurred out of, Doctor Steve Horvath lab at UCLA.

And really, in 2013, he created the first ever, sort of, epigenetic clock, as they say. And that was a clock which, which took, you know, a couple, you know, several hundred patients and, and really used these methylation marks to be able to predict their chronological age.

So it was meant to predict at least first their chronological age. And that algorithm wasn't necessarily medical at first. It was really used for things like, you know, forensic crime scene investigation where they were trying to see how old someone was at a crime scene, or, you know, even later, it was used to date refugees, for Syrian refugees to see if they were adults or minors and then therefore eligible for asylum.

And so it didn't necessarily, have a health context, at least at first. But what they started to see is that people who were generally older biologically or by this algorithm then, than they are chronologically, were at increased risk of several different diseases.

You know, one example I always give is cancer, where if for every one year you are older, biologically, even chronologically, for these algorithms, you would increase your risk of getting cancer, over the course of the next three years by 6%.

And you increase your risk of dying of cancer over the next five years by, essentially 17%. So so even just being a couple years older can be, you know, have drastic changes to your health.

And it all comes down to this idea that that aging is the number one risk factor for almost every chronic disease and death. And so if age is that good, then, you know, we all know age has its limitations.

Chronological age, at least we all know people in their 70s who look like their 50s and vice versa. So we've always known we needed a better measurement.

And at that point, when we started to see the link of these epigenetic measurements and these epigenetic clocks to health, we thought, hey, maybe this is a really good measurement to measure age.

And there've been several iterations of that. You know, I think the definition of aging is, you know, technically a progressive loss of function over time.

And that can be really hard to say. And so so these newer clocks, instead of training to chronological age, have been trained to predict, other measurements, particularly things like morbidity or mortality.

So we have things like clocks that can predict death or clocks that can really be associated with your level of disease or your propensity to get disease.

And so so these clocks have gotten better and better over time. They'll continue to get better and better. And so what we know now, though, is we have a way to really quantify this aging process that is a little bit new and novel and unique and really different than anything we've had before.

And so now that we can quantify this aging process, we can really try and work as best we can to try and reverse that aging process. And if we do, we can have some massive impact.

One of my favorite statistics to sort of mentioned to people is that if everyone in the world were to be seven years younger biologically than chronologically, we'd be able to cut disease in half.

50% of people would no longer be sick. You know, even if we just extended the lifespan by one year, we'd have over $250 billion worth of economic value.

And so those are the things that we're really trying to encourage. And we really feel like for the first time, this can be a scientific resource because we have an objective way to measure that aging process.

So it's really cool the way you think about aging, because it's like, age and aging are two different things.

Measuring Biological Age with Epigenetic Clocks

It seems like, because aging is literally could be seen as a condition, like a health condition, because you're unraveling, you know, everything your skin, your hair, your cells at a rapid pace.

So it's the pace at which you're sort of, you know, breaking down. That's you. It's an actual condition. And what you're saying is that you can measure this breakdown versus your age.

Meaning you see that person that says they're 70, but they look like they're 48, and you can figure out what what they're doing. Well, that's they haven't there are in aging it they don't have that condition.

Right. And people have to rewire reads the frame how they think about age versus aging. So in terms of, the work you do, I know you'd work with a lot of clinics.

How have they been able to use this as a tool to drive better outcomes? Yeah. You know, to speak to that, we absolutely think aging is a disease. Right.

And I think that, you know, people say you need to age gracefully and, and, and I think we want to flip that term around. Right. Because you don't necessarily need to age, you know, at all if we can help it.

Right. We really want to change that. But but you can absolutely sort of accept the, you know, the limitations of what it takes to sort of live a life which is, unfortunately, you know, a progressive loss of function, which we can't avoid, but we can slow it.

Right. And there are ways to do that. And so we absolutely believe aging is a disease. And even the ICD 11 has

now an extension code for age. So so even the traditional medical community is starting to, you know, accept this a little bit more.

And so, you know, in terms of our practitioners, we, we mainly work. Unfortunately, this test in aging itself is not a disease. So we work in sort of a cash pay model.

And in order to do that, the physicians that are definitely having the most success with our testing are the people who who definitively believe, I think like that philosophy we just mentioned that age itself is is something that can be measured and then also something that can be mitigated.

And so the physicians that work best with us are people who who really are treating health, at least preventatively, people who are thinking, hey, we really want to, you know, to, to fix this outcome.

And, and in order to do that, we want to take a measurement. We're going to implement changes into your life and see what works for you in the best way possible.

Do you think that because, I mean, you said the research is in its infancy. It's getting better. Do you think that we're going to get to a place where because epigenetic apps are so precise in terms of why things are happening, will it replace traditional blood work and how we think about what we even should be measuring for chronic conditions.

You know, I think that it's always not going to be perfect for blood work. But with that being said, there are already things that we can do now with this testing that, I think will improve medical care.

So already, for instance, we can predict things like, your telomere length. We can predict things like your Il6 or your TNF alpha, or your C-reactive protein.

So we can do all these things just through methylation measurements. Granted, right now they're not, I would say, as accurate as those other measurements.

But but they're getting there. We can right now even go ahead and tell you, you know, how many immune cell subsets you have, how many CD4 cells, how many CD8 cells to tell you how your immune system is functioning?

Again, these things need a little bit more vetting in order to be widely applicable. But, you know, not only can we read and program it to tell us other measurements, but we can even use it to tell us risk of disease, right?

How likely you are to have cardiovascular disease? Even recently, one of my favorite algorithms that came out were an algorithm that can actually diagnose schizophrenia.

And with around a 98% accuracy from, from Baylor. And, you know, the reason I like that is because, you know, schizophrenia, at least up to this point, has been a clinical diagnosis, right?

It's been something you have to go see your provider for. They have to, you know, assess you. But now we can actually see an objective marker in blood.

Right. And so it's a new concept where you know, the the epigenetics are actually signaling everything that's gone on in our lifetime and everything that's happening right now.

You know, one of the diagnostic criteria is, the imprint, or sorry that you say the exposome, which is, sort of a history of exposures that that you have over the course of time.

And so we can actually tell you how much pollution you've been exposed to, how much, you know, heavy metals you've been exposed to, and etc.. You know, the when we when we think about this stuff and we think about things genetically, we were kind of spoiled where, like you said, the researchers are a little further ahead. Right.

So where we speak with more sort of certainty about things, and it's really cool to be in this pioneering stage of

something that you're bringing to market that's going to sort of change the world.

Are you finding that there's resistance? Because we often find when things are new that there's certain practitioners, certain bodies that say that this isn't this is beautiful science.

I get this way for me. Yeah, definitely. And, you know, one of the biggest, a particularly and I would say this aging related criteria because aging itself, as you mentioned, is, is sort of shrouded with one problem, which is how do we define aging?

Right. You know, it can be sometimes difficult to define that progressive loss of function. And really, in order, one thing we're very certain of is that, that this advanced aging via these markers is associated with more disease and is objectively connected to every chronic disease.

And so we know that faster aging predisposes you or put you at a higher risk category for those diseases. What we don't know yet is that reversing these markers is associated with better health phenotypes.

And so so that is not been necessarily proven out, yet, although I think there's, there's a lot of evidence coming. You know, one of the things that we're trying to do is, prove that the things classically interventions, like, for instance, caloric restriction, which we know improve healthspan and improve lifespan, and we, we, we want to be able to have these clocks respond in the same way that we know caloric restriction does. Right?

And improving those lifespan. And so, we just have some, some data now from the calorie trial, which is a 25% caloric restriction diet over the course of two years.

And what we're seeing is that indeed, we are picking up those related changes. And so, so, so we're starting to build those data sets to say that, yes, if you reverse these metrics, you are picking up the fact that these are anti-aging.

And then we know those are associated with improved health phenotypes. And so so that is the process that's still ongoing. But the data looks really positive at least for now.

And you know people may not know this, but you actually participated in a lot of research like you just commented on a couple of them. But, a big part of your business is people using your tool to vet or prove out their research, which is interesting because it part of what is required to prove the point was the right measurement to begin with.

Right? You couldn't you couldn't measure scientifically. And now all of a sudden that you've made the tool available. So how has that been applied and various studies that you've been involved in.

Yeah. So so you know everyone is looking to you know, because age is so associated, everyone wants to turn back the clock. And so a lot of the work that we've been doing is interventional in nature, right?

Where we're comparing some of the best anti-aging strategies or some of the most exciting anti-aging strategies to see what happens to people who reverse those processes.

And then and then also trying to vet, you know, which therapy is better than the other one. Right? So we can actually say this is significantly anti-aging or this is, you know, anti-aging, but only mildly.

This is not good. And so the first published paper that we had was actually looking at the effects of Covid 19 and and also not just Covid 19, but there was mRNA based vaccines as well, where we were able to say, you know, those people who got sick with Covid, what happened to their aging?

And then also the people who took the mRNA based vaccines, what happened to their aging? And we saw some really interesting results there that we we, submitted for publication with Cornell and Yale, where we were able to, essentially see a very clear line of demarcation, people who got Covid and were under 50 actually saw a little bit of an anti-aging effect.

And we think that's because it stimulated their immune system, and they had a more robust way of dealing with that insult. However, people over 50, actually got older with Covid and it was a very clear line of demarcation.

And we think that's because obviously, as our immune systems get older and decline, they weren't able to mount as an appropriate immune response, and therefore they weren't able to sort of handle that insult, which was that infectious disease.

And strangely enough, even with the mRNA vaccines, we actually saw a very small, but statistically significant, anti-aging effect there as well. That's really interesting because it's it speaks to, for example, you know, to simplify for people, it's like going to the gym and you can stress the muscle and work it out, or you can damage it with the same exact action.

Right. And it just depends. What are you capable of handling, you know, what are you ready for?

Clinical Uses, Resistance, and Research Validation

And as you age you get to 50 depending on what your lifestyle was and how you maintain things. Well, you may not be ready for that. You know that impact anymore, right?

So, I know a lot of what you do. I should say the crux of it is around methylation markers. And then, you know, we've talked to so many people and everyone talks about methylation, but everyone has a different meaning or a different view or a different gene, different perspective on what even means.

Can you break down to us? What are we even talking about when we say methylation? What's important, what to look at? Yeah, absolutely. And you're exactly right.

Especially in this practitioner market, the functional market I think knows the importance of methylated co-factors. Right. Things like B-12 or or five methyl folate.

And they know the importance of genes in those locations too. Like, you know, the Com genes of our genes. And so a lot of times these clinical providers, you know, have thought about methylation in this context, right.

Do you have high homocysteine. Is that predispose you to some of these cardiovascular related outcomes. And so so that is absolutely an important part of methylation.

And it's still connected I should say correlated to what we're looking at. But what we're looking at is something entirely different. Not about your ability to methylation, but what on your DNA is or is not methylated.

And that's a very, you know, difficult conversation because your ability to methylation affects what genes are methylated. And so it can be, you know, sort of a chicken or the egg type situation here.

But but this is actually been looked at in regards to epigenetic aging, for instance. And so we actually know that, for instance, of women who have an MTT for six, seven, seven cc variant are predisposed to faster aging rates, than those who don't.

And actually, that can be fixed with a simple supplementation with, you know, D vitamins or folate. And so, so, you know, it's important to not just know your epigenetics, right?

Because we might be able to say, hey, you're a faster aging, but we wouldn't know that that would be a good recommendation unless we also had the genotype.

And so I think it's important to have have both there, in order to help influence your decision making process. But unfortunately, they're also two separate, different processes, people, you know, who are methylated well, or people who are not mitigating well are still going to have epigenetic features which are indicative of a completely different fixed.

Yeah. So it's kind of like, here's the marker, here's where you're at today. But then to know why genetically we'll find out where are you. Suboptimal. What's the thing.

What's that dial that needs to be turned to do this have a better outcome. Right. So it's like when you say that women are not faring as well because we find similarly with a lot of conditions, you know, for example, cardiovascular disease, women are much more likely to die on the first event than men.

I think it's 66% of women that get hit with some kind of heart attack. You know, literally in the first, instance with no previous symptoms or warnings, they're going to pass away, unfortunately.

But for men, it's a much smaller number. A lot of that we see and the research is continuing, compounded by estrogen toxicity and, you know, estrogen levels and estrogen dominance.

Is there anything epigenetic that speaks to that or is that research not done yet? So so the actually the there is a little bit of research, I should say, needs a lot more work, right?

Like a lot of the things we'll talk about today. But, you know, it's interesting to know that first off, just from an aging perspective, women always age better than men.

And that, you know, it backs up sort of what we know about women's health spans and life spans. Right. Which are generally better than men's. And so we actually see that, here in these epigenetic aging processes, we also know that particularly women, you know, after they go through menopause, actually tend to have much more accelerated aging.

So they tend to age at a much faster rate, even maybe than some of the men would. And so that's interesting. We also know that total lifetime estrogen exposure does have some correlations to epigenetic aging rates, especially of certain tissues where we know that, for instance, in the, you know, vaginal, endothelium tissue, estrogen might be anti-aging, but in other tissues, it might be pro aging.

And so unfortunately, though, the one thing we don't know is what type of estrogen metabolites, due to the aging process. So we don't know, you know, as you break down your estrogen, if some of those metabolites we know are associated with cancer might be positive aging or pro aging or, or negative aging, and so hopefully those studies will be done.

But but but definitely I know that a lot of our physicians we're taking our testing are getting those measurements. And so hopefully we'll be able to match those up. Yeah.

But we we've been learned in our research that you when you have a metabolite pre menopause it could be supportive and positive. But post menopause it actually speeds up the negative metabolite.

And it literally changes its function. So you know and there's things that we believe about things. And as you learn more research it completely flips itself on its head.

And we're saying the opposite of what we used to say, you know, to. Yeah. And I think that one of the things might help. That's all that is, is, is this more of this multi-omics analysis?

Right. So not just looking at genetics, not just looking at epigenetics, but also incorporating measurements like your transcriptomics and proteomics, metabolomics and, you know, microbiome.

I think that as we get a more complete picture of health, we'll be able to solve a lot of those questions. And so I think that, again, hopefully everyone is looking at these things in composite biomarkers rather than just, you know, a single thing all by itself.

So you bring up the microbiome, which is interesting because there's a couple companies out there that their current marketing campaigns basically are genetics laundering. Right.

Meaning if you know what's going on in your gut, you don't need to know anything else because there's more DNA of foreign entities in your gut than there are of yourself in your body.

So how did the two marry? It said, what's in your gut is important for obvious reasons, right? Your immune system is built here. Your your serotonin. Like there's so many things that are coming from the gut.

How does the things eventually connect or do they ever. Yeah. You know, I think that, you know, they absolutely connect, right. Which is that they they build who we are and what we're doing.

But the question is, is, you know, how do we value information? And I think until you get that information, in a certain scenario, in large numbers, it's really hard to know what's a prioritize.

But I think that, you know, generally in, in these, you know, wide association studies, I think that, you can start to see the connection between, you know, in genetics is well built out there where we know that, you know, a significant portion of of everything that we do is built on that underlying DNA sequence and how we interact with our environment.

And that, you know, you have to do it, I think, in the larger context of biochemistry, right, that central dogma where, you know, the DNA it creates, you know, mRNA and that imprint is regulated by epigenetic transcription.

Right. And, and then ultimately transcription, that transcription goes to peptides and proteins which build the infrastructure of our body. And then there have metabolites and those metabolomics are equally important.

So I think that in order to really marry all of those, you need to start getting that data at the same point in time. And doing that across multiple, different investigations.

And we're doing that I think, you know, even with genetic data, we're looking at the, the genetic input on to methylation pattern. So we can start to say, you know, these these methylation patterns might be a result of these genetic snips.

And, and then slowly start to inform our rationale for that. And so so again I think you just need to, to look at the whole picture as much as possible and whenever possible.

But again, it can be expensive to do so. It's not a quickly moving process. Yeah. And it sounds like the doctor the future is a connected doctor that's getting insights from all these various folks into this central hub, where all of our unique interpretation tools may eventually be obsolete, because you need the central hub that interprets everything and gives you one finite answer, you know, and that's what I've been working.

But that's eventually where things get to is interoperability. Integration, you know, how do you take all these beautiful sets of data and put them together?

And we'll get there eventually. And we already see that happening in the DNA world where there's people that are doing great things. Now, how do we take the genomics and combine that with this great thing and make something even better?

Right. So exactly. And I think that that, this whole idea of what we call the multi-omics, right, which are all those platforms, you need that data set together.

And, you know, there are a couple organizations, very few in the world who are actually doing this. But you look at, at Biobanks, like the UK Biobank or, you know, the interval study in the UK or Harvard Partner Biobank or the Health and Retirement Study.

These what they're able to do is save samples across multiple years so that we can really learn this data. And I think that, you know, as those data sets begin to build, the one big limitation has been how are we able to look at this information? Right?

You know, even from an epigenetic perspective, we're still, you know, one not even 1/29 of the way to the whole picture. Right? And so a lot of work needs to be done on, on the platforms itself, on how we look at these things.

But the data is starting to be generated. And so I think that that every practitioner in the future will start to see these multi-omics studies and then realize how to weight these things and how to look at them as a bigger picture.

So, you know, a lot of the people that are listening today, they're they're here to, you know, kind of I want to know what's wrong and how do I fix it, but how do I fix that part is the most important.

So I know that's not what you do. You're supporting, clinicians and consumers with information, but what have you sort of gleaned or learned from kind of listening in on success stories in terms of here's biological age, right.

And some people aren't doing so well. What are those few things that people should be doing that have been having an impact? Yeah. So so we do a lot epidemiologic epidemiology.

Because you know, these these these samples have been looked at for a long time and they said, hey, these better ages. What are they correlated with in these first ages.

What are they correlated with. And so we know a lot about that. You know, unfortunately though, I would say, what we found is, is relatively intuitive.

You know, it's generally the things we already know, right? So we know that, for instance, you know, better diets, right. Less, less, you know, carbs, less fats, you know, more protein tends to be, you know, better in the Mediterranean diet, for instance, is a great diet for epigenetic aging.

And so we know that generally that's recommended. But again, we the Mediterranean diet is one of the most well-studied diets in the world. And most people know it's a relatively healthy diet.

And so in addition to that, we know, that, you know, exercise is great.

Methylation, Multi-Omics, and Lifestyle Factors

Particularly cardiovascular exercise is great, but we also know that too much exercise is probably a negative thing. And so we see this in some of our Olympians or pro athletes where they exercise maybe too much, have too many reactive oxygen species and, and maybe have accelerated aging.

You know, we we see this with even behaviors like drinking or smoking. We know that smoking is one of the worst things you can do in order to drastically increase your age.

And we know from drinking, there's data that suggests that that, you know, 1 to 2 drinks of beer, wine per week is actually positive. And, and but, you know, doing too many drinks is actually a negative thing with people who are heavy drinkers being on average, 2.2 years older on average, than those people who are not.

And so from an epidemiological perspective, we know the importance of sleep, we know the importance of stress reduction. And so most of the things we see there are relatively intuitive.

But what's really exciting, what we're really starting to learn is more of that interventional data. Right. What are those, those the studies that look at, at baseline looking at treatment and then look at an outcome.

How are those changing these aging rates? And some of the work there just been fascinating. That's incredible. So what are some of the conditions that you looked at there.

Yeah. So, so so today there are about nine studies which have been longitudinally done, but we ourselves have over 15 underway. And so some of the most popular, I would say, are things, for instance, like, the first day that ever came out, looked at metformin, growth hormone in DHEA.

It's called the Trim trial. And really the whole goal was to regenerate the thymus or the immune system with age. And they did that via growth hormone.

And so but the next part they thought about was, you know, once we're, you know, sort of increasing growth hormone, how do we mitigate some of the side effects of growth hormone.

And for that, that was DHEA and metformin, which were used to help control the insulin resistance side effects of of have growth hormone. And so they did that in in a limited number of patients, was the first ever proof of concept study that you could reverse your epigenetic aging.

And so it only did it in nine patients, but it did it over the course of 1.5 years. And and over that, that time period, they were able to reverse epigenetic age on average in those patients by 2.5 years.

So 2.5 years of age reversal and 1.5 years worth of time. And if you remember that statistic from earlier where I said you know, if everyone in the world were to reverse their epigenetic age by, by seven years, you would essentially reverse, you know, cut disease in half.

That going 2.5 years is pretty significant. And so it was definitely very hopeful. And so that was the first ever proof of concept. But we even know simple things like vitamin D supplementation on average.

And this was done in overweight patients. But you know, just 4000 IU of vitamin D a day can reverse epigenetic age by 1.8 years. And that's over the course of just 16 weeks.

And so there, a lot of these studies which have been published, but I think that there are the studies which have been published and the studies which I think I'm most hopeful for, and those are a little bit different.

Those are a little bit more, I would say exotic, things, for instance, like plasmapheresis or young plasma transfers where you take plasma from a younger individual.

And then put it into an older individual for age reduction. And then probably the, you know, the one of the the biggest concepts, at least at this point, is this idea of epigenetic reprograming, where, you know, in 2012, there was a Nobel Prize given to, Doctor Yamanaka, who proved for the first time ever that you could take, a cell, a committed cell, and actually use growth factors to transition that back into a pluripotent stem cell.

And so you can actually, you know, the, I would say, did differentiate this into any cell in the body could go back to a pluripotent stem cell, which was, an amazing finding and obviously is why he won the Nobel Prize.

But the idea here is that whenever you do those, those reprograming, you also actually reset the epigenetic clock. You can take a, you know, a cell which has, age, let's just say of 50, and then reverse that to an age of zero.

And so the idea there is that you can maybe even cause rejuvenation of tissues, with these epigenetic reprograming. And, and many people might be familiar with this because it suddenly has recently gotten a ton of publicity in press because it actually created the biggest, well, most well funded startup of all time.

And Altos Labs, where Yuri Milner and Jeff Bezos funded this for over $3 billion. Right. So that's phenomenal because essentially what you're saying is do whatever you want to your body.

You can reprogram. So and so have a chance. You know, I think that that's definitely the hope. I would say that I'm not nearly that hopeful. You know, there's been some cool studies, though, particularly in animals where, you know, even Doctor David Sinclair at Harvard.

You know, expressed some of these in, in, in age, blind mice. So, so mice that had lost their, their vision as a result of age. And he was actually able to restore vision in these mice, by just expressing these factors and turning back maybe again, I don't know if the turning back of the original clock was the reason that it happened.

But but it was definitely a process that was, was also happened whenever, those other vision related changes happened. And so there's definitely a lot of reasons to be excited about about this marker of age and in quantifying this aging process.

But but with a lot of work needs to be done in order to make sure that we know the best interventions. And but those interventions can range from everything from these procedures to supplements to diet, nutrition to you know, sleep strategies and, and and so every area of the life impacts these epigenetics, which also makes it really hard to control. Right.

And so so we really need to be very careful about how we do these investigations and what recommendations we make. And I understand the theory and it's proven I mean, he won a Nobel Prize for the work.

How do you get the body to adopt it head to toe, you know, how do you take it from a cell on your dishes? It's that delivery, which I guess is why there's $3 billion on the table to figure out, right?

Yeah. You know, and it really, it starts with, you know, gene therapy. But one of the and so, you know, using, you know, viral vectors to, to put this into your DNA and express these factors.

The problem though is that there's been some literature that suggests that these factors can also be incredibly cancer causing. And so, you know, that's why this is a I think so, you know, scary.

But but I think that they're, you know, they're obviously well funded. And I think that they've also assembled one of the most amazing teams. You know, some of, you know, I mentioned Doctor Horvath, who was the first to create this epigenetic clock.

He's now on that team. You know, some other, of researchers like Morgan Levine and the filter are amazing. And to move this, epigenetic clock literature further than anyone else are all on that team, including Doctor Yamanaka himself.

And so so I think that they've got a who's who of the scientific community and, and definitely excited to see what happens in the coming years. That's pretty incredible.

So we know that that's where things are going, that eventually there's a pill you can take or switch. You can turn on or off, and you get to reset the clock.

And who knows if that's reserved for a lucky few or if everybody gets to try it out one day. But the the things that you're talking about that are more intuitive, like sleep, eat, etc., what kind of impact have you seen?

You know, when people sort of do things right, have you seen sort of an average of here's what you can expect? Yeah, definitely. I think it is slightly different from person to person. Right.

I think that, you know, for those people out there who take our test or pick a biological age test and they see that their age is accelerated, don't be too scared.

I think that's one of the takeaways I really want to mention, because generally it's easier to to to have a better impact on your epigenetic age if you're already accelerated for people who are who are doing really, really well, have year age gaps, sometimes it's a lot harder to influence change in those people.

And so so I think the idea here is for everyone, no matter where you're at, try and reduce this value as much as possible. But beyond that, I think, you know, you can really expect to see, you know, I would say several age related years of age related change with even just the proper diet, lifestyle, nutrition, especially if you start to identify things that you need more specific help.

And that's I think a lot of times where other lab measurements and even genetic testing are very helpful in identifying what your propensities are, making those changes, and then seeing that in your epigenetic age.

And so, you know, right now, epigenetics is not at the point where we can actually tell you, hey, you're nutrient deficient here or you nutrition deficient here, or you're more likely to have this or that.

As it relates to nutrition or diet or lifestyle, but we'll get there in the future. But right now, I think that using other platforms like, you know, traditional lab testing or even genetics are the best ways to go about that.

Yeah. So, you know, with what you're doing, I know that like, like we said, you work with a lot of clinicians. You're working also, the public can come too directly.

Is that possible or it's only through clinics. So so we do sell direct to consumer. But we I would always say that if you have the opportunity to go to a physician to do this, absolutely. Do it.

Not only do they get more reporting, just legally we're able to offer a little bit more to physicians, but it's also a little bit easier to understand the process.

I would say with, with someone who has some, some medical expertise because it's still new, it's still complicated. And, you know, and, and honestly, a lot of physicians, even in the traditional medical space, never heard about epigenetics when they were going through school.

And so it really requires, I think, a practitioner who's is educated in forefront thinking. And so you can't get it from us directly, but it's not as robust as you would through a physician. Yeah.

So that's exactly what I wanted to ask you, was that, you know, when a consumer orders, you know, we often find that when it comes to, meaningful data, like what you provide, that it requires some level of interpretation and also considering your context and, you know, other, other information about yourself in combination with it to be truly actionable.

So, you know, like you said, people in order, but it's good to have someone partnered with you to sort of quarterback that.

Interventions, Reprogramming, and Future Applications

And I'm sure you could recommend if somebody wants somebody to work with. Right? Yeah, absolutely. And so we have, we have, people we'd recommend who do a lot of our testing in a telemedicine format.

We have people if you want to visit locally. We've got networks all around the United States and even globally. Now we're starting now to offer testing in Canada, parts of Europe, in Southeast Asia, as well as New Zealand and Australia.

And so, no matter where you are listening to this, if you if you'd like to perform some of this testing, we can definitely give a recommendation on the best providers to work with.

And so, you know, we still have a lot to talk about. But where do people go to to find a test. Yeah. So you can go to true diagnostic true diagnostic.com.

And and you can even buy it from there. Or you can reach out to us at support at Tru diagnostic.com. And we're happy to give you recommendation on, on a provider you can work with to get this testing okay.

So we'll put that into the notes make sure people have access to it. But one thing that I know, so prior to your work, if you went to a functional medicine or sort of an integrative clinic and you wanted to measure biological age, they would typically direct you to telomeres.

Yeah, absolutely. So what's the is there variability there or are you getting the same outcome. Or is this is that one piece of the story. Yeah. So so it's important I think, to mention that, you know, telomere attrition is absolutely a hallmark of aging as is epigenetic dysregulation.

And so, you know, they're both important and they're both separate. Right. If we you know, we've already talked about resetting that epigenetic age in a cell.

If we were to reset the epigenetic age, we'd still see telomere length shortening. And vice versa. If we were to immortalize telomeres, we would still see epigenetic aging.

And so two very distinct processes. However, you know, one of the biggest limitations with telomere length testing has been its level of of usefulness as a predictive tool.

You know, there's a paper from 2017 which compares biological age predictors, and its summary on telomere length is that that all the telomere length is extensively validated.

It has relatively low predictive power, meaning that if you have low telomere length, it doesn't necessarily tell us what will happen. Right. And I think that that has been a serious limitation.

And so comparing these two, there's a recent study done looking at genetically identical twins and it said, hey, out of the the the difference in the phenotypic aging of those twins.

Right. How are the aging what percentage of that is probably due to telomere length. And it came up with right around 2% of all of that phenotypic variation is digital in length, whereas vice versa.

I looked at the epigenetic aging and it came up with right around 35%, of phenotypic aging. And so so I don't ever want to say the mere length is not important.

It definitively is. It's a hallmark of aging. But as we're comparing maybe the impact, I would say that telomere length is probably a little bit less effective than, or less important to predicting outcomes, than, than some of those epigenetic ages.

And so, with that being said, even in our testing, we're actually able to to estimate the methylation, the length of your telomeres. And so we can generally tell you where you stand in the population.

We can give you an estimated telomere age. And again, although we don't prioritize it as much, on the review, we would generally say it's an important part of biology that you can't necessarily ignore.

And it sounds like telomere testing is a much more static science, meaning you got what you got where epigenetics is just starting and there's so much more we're going to know, you know, that same data set that you have today, maybe much more information is going to come out of it a year from now.

Yeah. You're exactly right. That brings up a really good point that I forgot to mention is that as new data comes out, we traditionally will add more reports.

So we actually add a new report about every four weeks based on new data that we just didn't know we could interpret prior to then. And so, you know, even in the last few weeks, we've added, are you likely to lose weight with caloric restriction?

And we've added a mitotic clock, which tells you the number of stem cell proliferation you're going through per year. And so so we're learning more and more about this in the algorithms are getting better and better and better.

And so this data set will continue to grow. And actually right now we measure, you know, the 900,000 locations in the genome. But for all of our reporting we still use less than 2500.

And so just to give you an idea of, you know, how much more information there is left out there, you know, the it is very, very robust. And you can imagine that this will be a data set that continues to give over time.

And I think your answer is going to be similar, but, you know, there's also a camp that believes in aortic stiffness,

and that's a true measure of age.

And there's a there's a tool I don't know what it's called, what you put on your finger. And it measures some kind of pulse to determine aortic sort of aging as a what's called the hallmark.

And the thing about it is it's highly variable, meaning that, on today, you could be 65, but in a week you could be 60 and then back up to 70. It's kind of like a day to day measure of the impact of your decisions, to be familiar with tools like that and how important they are.

Yeah, definitely. And I think that, so even, you know, Prince, that's all I think, one of the big things about our tool is it not nearly as changeable as that.

It's not like you're going to see a 15 year age reversal, all of a sudden, which I actually think is a positive thing, because I think that what you're really seeing is an aging signal and not necessarily, you know, I would say a day to day, you know, view of how well you're functioning.

But but you know, this, this marker of epigenetic methylation just generally can be trained to predict even some of those physical measurements. So, for instance, you know, even some of our aging calculators are, you know, correlated to surface area or thickness of the brain, right, cortical thickness of the brain.

And so we can actually these measurements have even been shown that they can be related to physical measurements as well. And so not to say that it will ever overtake some of those really important values, you know, like for instance blood pressure.

Right. But but we might be able to give an overall idea of, of your, you know, your blood pressure over a longer period of time with some of these measurements, almost like a, you know, HbA one C for your blood pressure and, and see for your hormone levels versus your, you know, intermediate hormone levels.

And so, so the methylation is just again dependent on data generation. Methylation by itself is useless. You need to be able to link it to those clinical covariates cohorts.

And so all of that testing is is definitely paved the way. But I think that as time gets, you know, sort of going, oh, a lot of those, those measurements can be trained through methylation.

So you can use one test to predict multiple different areas of your health rather than, you know, taking, you know, 15 different lab values. Is there any work being done right now on, genetic expression of neurochemicals and what's going on in the brain?

Because I find that that's an area that's highly impactful because you're taking this such a gray, you know, let me ask you five questions and try and diagnose you versus something empirical, like the actual chemicals of your brain.

Genetically, we understand the pathways and what drives them. But you know this in time measurement. We don't know how to do that. So is there any work being done there.

Yeah. So so there are. But but there's one big limitation which is that, you know, as I mentioned, for epigenetics, a lot of this this is tissue dependent.

Right. And in order to get tissue from the brain, you you really need, you need someone to be dead or to have some type of brain procedure which already is, is a problem.

Right. And so so with that being said, there are absolutely algorithms which are correlating to brain function and actually, as I mentioned with schizophrenia, you can actually see very, very clear methylation patterns for things like depression or PTSD.

You know, they're actually just four loci that can differentiate current PTSD versus former PTSD. And so there are certain patterns and things that we're seeing with certain types of neurological diseases.

But, you know, always be a limitation that we're not measuring the tissue directly. And that's that's always going to be a little bit of a problem. You know, one of my favorite areas of research that we're doing, and this is going to be I would say, not super clinically relevant, at least any time in the future, is this idea of the imprint home.

And the imprint home is, is basically a set of, of epigenetic patterns that you only get from one parent. And so if we know anything from genetics, we know that if you get only one copy, you know, it can sometimes cause some big issues because it can be incredibly penetrable to disease.

But we actually have the same type of inheritance patterns for things epigenetic as well. And particularly those genes are incredibly correlated to, to neurological diseases.

Almost every neurological disease can be traced back to some types of patterns in this imprint, region. And so, the problem with this is that the imprint, is really never been described, ever.

We don't really know what genes are imprinted in, because in order to do that analysis, we have to have DNA from the parents. And we have to have DNA from a child to know what epigenetic patterns are changing.

And so for the first time ever, we're going to be, working with the, researchers at NC state, to to publish the first ever full list of human imprint, gene regions.

And so we're really, really excited about that because for the first time ever, we can start to see how these regions are associated with things like Alzheimer's or, or autism, even, or even, you know, outside of neurological diseases, things like obesity.

And so this is a really good marriage of of, you know, the traditional genetic framework, but also looking at the importance of these, these, these epigenetic expression patterns, which can, for instance, be changed by things like socioeconomic status or prenatal stress, how stressed you are in the womb.

And so there might be even easy lifestyle interventions, which could happen to to change your propensity for Alzheimer's much later in life. And so we're really excited about that. As an area of research.

And and again, it's not going to be super clinically useful at least yet. But over the course of the next 4 or 5 years, we're going to find out about things, about these neurological diseases that we just never knew.

That's really cool. And, you know, speaking of like trauma and genetic expression, there's a study that often gets quoted about the, descendants of the Holocaust survivors and then literally as a genetic legacy, inheriting the, you know, sort of genetic expression variability of what their parents experienced in that extreme trauma.

And so it's actually translates into the next generation. Yeah. Yeah, it's going to be pretty impactful. So we're sorry I just want to jump in there as well.

They just did another follow up study with the Rwandan genocide. And they see the exact same thing. The trauma from those can be up to it can even transmit themselves up to four generations later, which is incredible.

And even, you know, periods of famine. We can actually see that in the epigenetic expression of, of, of descendants up to four generations later, which is incredible.

And so even even how you live your life, you might think, hey, it's not going to impact my children, but but it absolutely will. You know, you can actually see how some of those things translate is really incredible.

So how do you see I mean, there's so much potential in what's going on in the science and in this industry. And you've come in, you know, right at the beginning and your part of what's driving the innovation.

So where is two diagnostics going to be in five years? Are you going to find that switch to turn on and turn off and add 50 years to someone's life? What's going to be going on?

Yeah. You know, I think that for us, one of one of the things that we're really blessed with is a lot of great, practitioner partners where, you know, they're generating data sets that are not typically found in your, your, you know, university data sets.

They're taking hormone levels. They're doing these things. And so I think that in order for us to be successful, we want to leverage some of those resources to create better predictive algorithms.

The first step in being able to, you know, treat, a lot of these things is being able to diagnose a lot of these things. And so the algorithms creating the algorithms to identify certain disease subsets, are really our first priority.

And then, you know, as we're doing with aging, where those aging algorithms have already been really well built out, we're really then at that point, starting to look at ways to go ahead and start treating that and being able to make recommendations on what to do and what not to do through a lot of those providers.

And so, so for us, we definitely want to drive the field of diagnostics forward, implementing, you know, as much as possible. But you know, our data set, which is, you know, one of the largest private epigenetic data sets in the world.

And so we really want to, to build those predictive algorithms, to make sure that that people in all areas of medicine can, can really benefit from them.

Yeah. That's a that's amazing because you know what you're doing. You know in pioneering you have to create it. It's not like there's somebody telling you here's the path.

You know you're you're building the path and you got the arrows in your back, you know as you're heading down that path. But ultimately 4 or 5 years from now, you would have built something that may shift the way we practice health care, you know?

So there's you diagnostically, which opens the door to therapeutics that maybe wouldn't have been possible because you're looking at the condition differently.

So you're providing, again, that open door to say, now go fix this thing. Right. If I figure out a better way to fix it, that's exactly the the idea is that, you know, once we again, what we can't manage, what you can't measure.

And for us, being able to predict and measure those things is of utmost importance because it gets you to that second question, which is, what do we do about it?

And that's really where the rubber hits the road. Yeah. That's awesome. So I just want to repeat for everybody. So to get to work with you on testing, it's true diagnostics.

And it's true. That's so true. Diagnostic takes with us you know just diagnostic singular true diagnostic Dicom. And and again, you can always reach out to us at support at Tru diagnostic Dicom or email me directly Ryan at True diagnostic.com.

Perfect. This was incredible. Matt, I'm sure that you opened everybody's eyes and ears to what epigenetics really is, that thing that they've been hearing the buzzword but don't really get what's going on.

So thank you for joining us. Highly informative. It was awesome to talk to you. Yeah. Always a pleasure. And thanks so much for having me.