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YOUR DNA

A Deep Dive Into The Science of Epigenetics

Kashif Khan interviewing
Ryan Smith

Kashif Khan
All right so, we've been talking a lot about genetics and the impact of genetics, cause 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. Where do I need to focus? What's broken? Where your epigenetic speaks to that and everything we've been speaking about epigenetically up until now has been more about the choices. Meaning what do I eat? How do I exercise is versus what do I measure? That's what's been missing for some time because to measure has been so complex. So who's joining us today, Ryan Smith, he runs Trudiagnostic, which a lot of you have already heard of, maybe even have tried to testing out, to determine your biological age, with very specific markers. What's going on in the inside? And then exactly where you need to focus. Ryan, thanks for joining us.

Ryan Smith
Yeah, thanks so much for having me Kashif. I appreciate it.

Kashif Khan
Yeah. This question always comes up. It's you know, What is epigenetics? Why epigenetics? Why not epigenetics? Why are you only telling me 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 out there. So tell us in a nutshell, what do people need to know about what their epigenetics can tell them?

Ryan Smith
Yeah, 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 on 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. It's epi obviously means above the genome. And so these are changes of tapping above the genome to regulate gene expression. And so as you mentioned, Kashif, this is still a very very new field. This is, you know, something 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 with 450,000. 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 genetics has had over the course of multiple decades. 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 an 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.

Kashif Khan
So how variable is that when you say like, you know, there's switches that get turned on or off, are 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, any given second in your cells. So is it that level of variability?

Ryan Smith
So it depends on the location. There's some locations in your genome which are widely changed. Others which almost never change. And so it all depends on the location. It also can generally depend on the cell type, 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 solely 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 gene off or turn gene on permanently. And so every cell type is different, which is actually one of the biggest limitations, in epigenetics as well.

Is because not only do we have to worry about, you know, the actual sequence in our accuracy of that diagnostic. We also have to worry what cells we're getting and how we control for those differences. And then again as you mentioned, how fluctuating are those se sequences? If one sequence is taken in the morning and one, two sequence is taken at night and they're very different, then that can be, you know, real pretty problematic to create any insightful information. And so, you know, the benefit of epigenetics is that they're temporal. Right? You can see changes in real time. But that's also a big problem in getting really accurate research.

Kashif Khan
So there's the sort of in time variability, but then there's the permanent change. And do we know yet how that happens? Meaning that this cells a heart cell and only accesses a certain piece of the genetic instruction manual so that it can operate as a heart cell. Do we understand that yet? How that happens?

Ryan Smith
Yeah, 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 at Trudiagnostic 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 you 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 you need to make are you're doing those investigations in the right way with very clear interlineated outcomes. And so, again right now it's a little bit less actionable than your traditional genetics. Right? I mean, we just don't know enough definitively about some of these features, but we're starting to learn. And aging is definitely again putting forward the majority of the research in that area.

Kashif Khan
So you, I mean, you do it when you build this business and this research company and your focus or primary purpose for which clinicians work with you is around aging in 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 this is the most useful function? And how do you even determine what biological age is?

Ryan Smith
Yeah, it's a good question. You know, this is a, I wish I could say I could take the credit for this, but you know, I think that the majority of this research was really spurred out of Dr. 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 took, you know, a couple, you know, several hundred patients, and really used these methylation marks to be able to predict their chronological age. So it was meant to predict at least first their chronologic age. And that algorithm wasn't necessarily medical at first. It was really used for things like, you know, forensic crime scene investigations, where they were trying to see how old someone was at a crime scene, or you know, even later it was used to refugees, theory in 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 they are chronologically, we're 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, then chronologically for these algorithms, you would increase your risk of getting cancer over the course of the next three years by 6%. And you'd increase your risk of dying of cancer over the next five years by essentially 17%. 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 aging is the number one risk factor for almost every chronic disease in 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 seventies who look like their fifties 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 from these epigenetic clocks to health, we thought hey, maybe this is a really good measurement to measure age. And there have 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 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 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 that 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 mention to people is that if everyone in the world would 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.

Kashif Khan
So it's really cool the way you think about aging, cause it's like age and aging are two different things. 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, 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't figure out what where they're doing well. That's, they haven't, they're not in aging yet. They don't have that condition, Right? And people have to rewire and read 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?

Ryan Smith
Yeah, You know, to speak to that, we absolutely think aging is a disease, right? And I think that, you know, people say, Hey you need to age gracefully. And I think we wanna 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 wanna change that. But you can absolutely sort of accept the, you know, the

limitations of what it takes to sort of live the life. Which is unfortunately there, 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 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 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 definitively believe I think like that philosophy we just mentioned that age itself, 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 really are treating health, at least preventively. People who are thinking, Hey we really want to, you know, to fix this outcome. And in order to do that, we wanna take a measurement. We're gonna implement changes into your life and see what works for you and in the best way possible.

Kashif Khan
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 gonna get to a place where, because epigenetics 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?

Ryan Smith
Yeah you know, I think that, it's always not gonna 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 . We can predict things like your IL-6 or your TNF alpha, or your C-reactive proteins. 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 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 to have cardiovascular disease. Even recently, one of my favorite algorithms that came out, were an algorithm that could actually diagnose schizophrenia and with around a 98% accuracy 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 a 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 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 imprintome or, sorry, I should say the exosome, which is a, sort of a history of exposures, 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 et cetera.

Kashif Khan
Hmm. You know, the, when we think about this stuff and you think about things genetically, we were kind of spoiled. Where like you said, the research is 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 gonna sort of change the world. Are you finding that there's resistance? Cause We often find when things are new, that there's certain practitioners, certain bodies that say that this isn't, this is science. Now get this away from me.

Ryan Smith
Yeah, definitely. And you know, one of the biggest, particularly and I would say this aging related criteria, because aging itself, as you mentioned, is sort of straddled 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 we, one thing we're very certain of is 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 puts 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 that has not been necessarily proven out yet. Although I think 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, clock restriction. Which we know improve health span and improve lifespan. We want to be able to have these clocks respond in the same way that we know clock restriction does. Right? In improving those lifespans. So we just have some data now from the calorie trial. Which is a 25% clock 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 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 that we know those are associated with improved health phenotypes. And so that is the process that's still ongoing, but the data looks really positive, at least for now.

Kashif Khan
And yeah, people may not know this, but you actually participate 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 it is required to prove the point was the right measurement to begin with. Right? You couldn't, hopefully you couldn't measure scientifically. And now all of a sudden that you've made the tool available. So how has that been applied in various studies that you've been involved in?

Ryan Smith
Yeah, 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 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, or this is not good. And so the first published paper that we had was actually looking at the effects

of covid-19. And also not just covid-19, but those 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 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 antiaging 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 there 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 based vaccines, we actually saw a very small, but statistically significant anti-aging effect there as well.

Kashif Khan
That's really interesting. Cause 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? 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 the, you know, we've talked to so many people and everyone talks about methylation. But every one has a different meaning or a different view or a different gene different perspective of what it 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?

Ryan Smith
Yeah, absolutely. And you're exactly right. Especially in this practitioner market. The functional market, I think knows the importance of methylated cofactors right. Things like B12 or, or 5 methylfolate. And they know the importance of genes in those locations too, like, you know, the

COMT genes or the MTHFR 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 predisposing you to some of these cardiovascular related outcomes? And 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 methylate. But what on your DNA is, or is not methylated. And that's a very, you know, difficult conversation because your ability to methylate affects what genes are methylated. And so it can be, you know, sort of a chicken or the egg type situation here, but this is actually been looked at in regards to epigenetic aging for instance.

And so we actually know that for instance, women who have an MTHFR 677 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, or a folate. And so, you know, it's important to not just know your epigenetics. Right? Cause we might be able to say, Hey, you're at faster aging, but we wouldn't know that would be a good recommendation unless we also had the genotype. And so, I think it's important to 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 methylating well or people who are not methylating well are still gonna have epigenetic features, which are indicative of a completely different things.

Kashif Khan
Hmm, Yeah. That's what it's kind like, here's the marker, here's where you're at today. But then to know why genetically we'll find out where you are 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 funny 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 gonna 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 epigenetically that speaks to that? Or is that research not done yet?

Ryan Smith
So actually there is a little bit of research. I should say. It 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 lifespans. 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.

And 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 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 negative aging. And so hopefully those studies will be done, 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.

Kashif Khan
Yeah. We've even learned in our research that 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 functioning. 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.

Ryan Smith
Yeah, definitely. Yeah, and I think that one of the things might help that solve that is this more of this multi analysis. Right? So not just looking at genetics, not just looking at epigenetics, but also incorporating measurements like, transcriptomics and proteomics metabolomics and 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.

Kashif Khan
So you, you bring out the microbiome, which is interesting because there's a couple companies out there that their current marketing campaigns basically are genetics slandering. 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 does the two marry, it's a what's in your gut is important for obvious reasons, right? Your immune system is built here, your serotonin, like there's so many things that are coming from the gut. How do the things eventually connect or do they ever?

Ryan Smith
Yeah, You know, I think that, you know, they absolutely connect. Right? Which is that they built who we are and what we're doing. But the question 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 to prioritize. But I think that, you know, generally 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 everything that we do is built on that underlying DNA sequence and how we interact with our environment. And then, you know, you have to view it, I think in the larger context of biochemistry. Right? That sinful dogma, where, you know, the DNA, it creates, you know, mRNA and that mRNA is regulated by epigenetic transcription. Right? And then ultimately transcription that transcription goes to peptides and proteins which will be infrastructure of our body and then they are 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 genetic input on methylation patterns. So we can start to say, you know, methylation patterns might be result of these genetic SNPs and then slowly start to inform, our rationale for that. And so again, I think you just need 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.

Kashif Khan
Yeah. And it sounds like the doctor of the future, is a connected doctor. That's getting insights from all these various spokes into the 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 not being worked up. That's eventually where things get to is interoperability integration. 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.

Ryan Smith
Exactly. And I think that this whole idea, what we call the multi omics. Right? Which are all of 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 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 one 29th of the way to the whole picture. Right? And so a lot of work needs to be done, on the platforms itself on how we look at these things, but the data is starting to be generated. And so I think that every

practitioner in the future will start to see these multi studies and then realize how to weight these things and how to look at them as a bigger picture.

Kashif Khan
Hmm. So, you know, a lot of the people that are listening today, they're here to, you know, kind of, I wanna know what's wrong and how do I fix it? 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 listing 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?

Ryan Smith
Yeah. So we know a lot epidemiology because, you know, these samples have been looked at for a long time and they said, Hey, these better ages, what are they correlated with? And these worse 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 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 you know, carbs, less fats, you know, more protein tends to be, you know, better. The Mediterranean diet for instance, is a great diet for epigenetic aging. And so we know that generally that's recommended, but again, the Mediterranean diet is one of the most well studied diet 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, 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 then maybe have accelerated aging. You know, 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 to suggest, that, you know, one to two drinks of beer wine per per week is actually positive. And but, you know, doing too many drinks is actually a negative thing, which 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 studies that look at a baseline, look at a treatment and then look at an outcome. How are those changing these aging rates? And some of the work there has just been fascinating.

Kashif Khan
Hmm. That's incredible. And so what are some of the conditions that you looked at there?

Ryan Smith
Yeah, so to date, 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 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 they chose DHEA and metformin, which were used to help control the insulin resistance side effects of growth hormone. And so they did that in a limited number of patients.

It was the first ever proof of concept study that 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 over that time period, they were able to reverse epigenetic age on averaging those patients by 2.5 years. So 2.5 years of age reversal in, in 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 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. 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 are a lot of these studies which have been published. But I think that there are the studies that you've been published and then studies which I think are 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, one of the biggest concepts, at least at this point is this idea of epigenetic reprogramming. Where, you know, in 2012, there was a Nobel prize given to Dr. 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 could actually, you know, I would say, 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 reprogramming, you also actually reset the epigenetic clock. You can take a, you know, a cell which has a age, let's just say a 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 reprogramming. And many people might be familiar with this because it suddenly has recently gotten a ton of publicity and press because it actually created the biggest, most well funded startup of all time in Alto's labs where Yuri Milner and Jeff Bezos funded this for over 3 billion dollars.

Kashif Khan
Right. So, wow that's phenomenal because essentially what you're saying is do whatever you want to your body. You can reprogram your cells and start over and have a second chance.

Ryan Smith
You know, I think that's definitely the hope. I would say that I'm not nearly that hopeful. You know, there's been some cool studies. Particularly in animals where, you know, even Dr. David Sinclair at Harvard, you know, expressed some of these in age blind mice. So mice that had lost

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 epigenetic clock was the reason that it happened. But it was definitely a process, that was also happened whenever those other vision related changes happened. And so there's definitely a lot of reasons to be excited about this marker of age and quantifying this aging process. But a lot of work needs to be done in order to make sure that we know the best interventions. But those interventions can range from everything from these procedures to supplements, to diet nutrition, to you know, sleep strategies. And so every area of life impacts these epigenetics, which also makes it really hard to control. Right? And so we really need to be very careful about how we do these investigations and what recommendations we make.

Kashif Khan
Yeah, and I understand the theory and it's proven. I mean, he wanna know about 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 and a Petri dish? So it's that delivery, which I guess is why there's 3 billion on the table to figure it out. Right?

Ryan Smith
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 put this into your DNA and express these factors. The problem though is that there's been some literature that suggest these factors can also be incredibly cancer causing. And so you know, that's why this is, I think so, you know, scary but I think that they're obviously well funded. And I think that they've also assembled one of the most amazing teams. You know, some of, I mentioned Dr. 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 in the field who are amazing and have moved this epigenetic clock literature further than anyone else or all on that team. Including Dr. Yamanaka himself. And so I think that they've got a who's who of the scientific community, and definitely excited to see what happens in the coming years.

Kashif Khan
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 things that you're talking about that are more intuitive, like sleep, eat, et cetera. 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 could expect?

Ryan Smith
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 wanna mention, because generally it's easier, to have a better impact on your epigenetic age, if you're already accelerated. For people who are doing really, really well have multi-year age gaps, sometimes it's a lot harder to influence change in those people. And 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 and nutrition.

Especially if you start to identify things that you need need more specific help on. And that's why I think a lot of times where other lab measurements and even genetic testing are very helpful in identifying what your propensity are, making those changes and then seeing that in your epigenetic age. And so, you know, Right now epigenetic is not at the point where we can actually tell you, Hey, your nutrient deficient here, or your nutrient deficient here, or you're more likely to have this or that as it relates nutrition or diet or lifestyle. but we will 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.

Kashif Khan
So, you know, with what you're doing, I know that like we said, you work with a lot of clinicians you're working also the public can come too directly. Is that, that possible, or it's only through clinics?

Ryan Smith
So, so we do sell direct to consumer, but 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 someone who has some medical expertise, because it's still new, it's still complicated. And, you know, 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 educated for forefront thinking. And so you can't get it from us directly. But it's not as robust as you would through a physician.

Kashif Khan
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 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. And I'm sure you could recommend if somebody wants somebody to work with.

Ryan Smith
Absolutely. And, and so we have people we'd recommend who do a lot of our testing in a telemedicine format. We have people, if you wanna 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 south east Asia, as well as New Zealand and Australia. And so no matter where you are listening to this, if you'd like to perform some of this testing, we can definitely give a recommendation on the best providers to work with.

Kashif Khan
And sorry, you know, we still have a lot to talk about, but where do people go to find the test?

Ryan Smith
Yeah. So you can go to True Diagnostic Trudiagnostic.com and you can even buy it from there or you can reach out to us at support@trudiagnostic.com. And we're happy to give you recommendation, on a provider you can work with to get this testing.

Kashif Khan
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.

Ryan Smith
Yeah, absolutely.

Kashif Khan
So what's the, is there variability there? Are you getting the same in outcome or is that one piece of the story?

Ryan Smith
Yeah, so it's important I think to mention that 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 were, 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 shortening. And vice versa if we where 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 testing has been its level 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 although 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 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 those, the difference in the 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 phenotype variation is due to telomere length. Whereas vice versa. I looked at the epigenetic aging and it came up with right around 35% of aging. And so I don't ever wanna say telomere length is not important. It definitively is, it's hallmark of aging. But as we're comparing maybe the impact, I would say that telomere length is probably a little bit less effective or less important at predicting outcomes, than some of those epigenetic ages. And so with that being said, even in our testing, we're actually able to estimate via methylation the length of your telomere. 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.

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

Ryan Smith
Yeah, you're exactly right. And 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 clock 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 we're learning more and more about this and 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 2,500. So just to give you an idea of, you know, how

much more information there is left out there, you know, it is very, very robust, and you can imagine that this will be a data set that continues to give over time.

Kashif Khan
Hmm. And I think your answer's gonna 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 tool. I don't know what it's called, but you put it on your finger and it measures some kind of pulse to determine aortic sort of aging as a what's called a hallmark. And the thing about it, it's highly variable, meaning that, 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. So I dunno if you're familiar with tools like that and how important they are.

Ryan Smith
Yeah, definitely. And I think that, so even, you know, that tool I think one of the big things about our tool is it's not nearly as changeable as that. It's not like you're gonna see a 15 year age reversal. All of a sudden, which I actually think is a positive thing, because I think that the, what you're really seeing is an aging signal and not necessarily, you know, would say a day to day view of how well you're functioning. But you know, 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 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'll ever overtake some of those really important values, you know, like for instance, blood pressure. Right? But we might be able to give an overall idea, of your, you know, your blood pressure over a longer period of time, with some of these measurements. Almost like a, you know, Hba1c for your blood pressure or an Hba1C for your hormone levels, versus your intermediate hormone levels. And 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 variates, covariate. And so all of that testing, is definitely paved the way. But I think that as time gets, you know, sort of going a lot of 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 15 different lab values.

Kashif Khan
Hmm. Is there any work being done right now on a genetic expression of neurochemicals and what's going on in the brain? Cause I find that, that's an area that's highly impactful. Cause you're taking this so 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 this in time measurement. We don't know how to do that. So is there any work being done there?

Ryan Smith
Yeah, so there are but there's one big limitation. Which is that, you know, as I mentioned for epigenetics, a lot of these, this is tissue dependent. Right? And in order to get tissue from the brain, you really need, you know, someone to be dead, or to have some type of a brain procedure. Which already is a problem right? And so with that being said, there are absolutely algorithms which are correlating to brain function. And actually it, as I mentioned with schizophrenia you can actually see very, very clear methylation patterns for things like depression or PTSD. You know, there're actually just 4 low signs that can differentiate current PTSD versus former PTSD.

And so there are certain patterns in things that we're seeing with certain types of neurological diseases. But it'll always be a limitation that we're not measuring the tissue directly. And that's always gonna be a little bit of a problem. You know, one of my favorite areas of research that we're doing, and this is gonna be, I would say, not tradi super clinically relevant at least in new time in the future. is this idea of the imprintome. And the imprintome is basically a set 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. Cause it can be incredibly penetrable to disease. But we actually have the same type of inheritance patterns for things epigenetically as well. And particularly those genes are incredibly

correlated, to neurological diseases. Almost every neurological disease can be traced back to some types of patterns in the imprintome region. And so the problem with this is that the imprintome has really never been described ever. We don't really know what genes are imprinted. And cause in order to do that analysis, we have to have DNA from the parents and we have to have DNA from the child to know, what epigenetic patterns are changing. And so for the first time ever, we're gonna be working with researchers at NC state, to publish the first ever full list of human imprintome 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 autism even, or even, you know, outside of neurological diseases, things like obesity. And so this is a really good marriage of, you know, the traditional genetic framework. But also looking at the importance of 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 change your propensity for Alzheimer's much later in life. And so we're really excited about that as an area of research. And again it's not gonna be super clinically useful at least yet. But over the course of the next four or five years, we're gonna find out about things about these neurological diseases that we just never knew.

Kashif Khan
Hmm 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 them literally as a genetic legacy inheriting the, you know, sort of genetic expression variability of what their parents experienced and that extreme trauma. And so it's actually translates into the next generation.

Ryan Smith
Yeah.

Kashif Khan
Yeah, can be pretty impactful. So.

Ryan Smith
Yeah absolutely. Sorry 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 it 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 descendants up to four generations later, which is incredible. And even how you live your life, you might think, Hey, it's not gonna impact my children. But it absolutely will. You know, you can actually see how some of those things translate.

Kashif Khan
That's 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 you're part of what's driving the innovation. So where is tru diagnostics gonna be in five years? Are you gonna find that switch to turn on and turn off and add 50 years to someone's life what's gonna be going on?

Ryan Smith
Yeah, You know, I think that for us, 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, you know, university data sets they're taking hormone levels they are doing these things. And so I think that in order for us to be successful, we wanna 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 for us, we definitely wanna drive the field of diagnostics forward implementing, you know, as much as possible the, you know, our data set, which is, you know, one of the largest private epigenetic dataset in the world. And so we really want to, build

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

Kashif Khan
Hmm. Yeah. And that's amazing cause you know what you're doing, you know, and pioneering, you have to create it. It's not like there's somebody telling you here is the path, you know, you're building the path and you got the arrows on your back as you're running down that path. But ultimately four or five years from now, you would've built something that may shift the way we practice healthcare. 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? To figure out a better way to fix it.

Ryan Smith
That's exactly 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 the those things is about most 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 through.

Kashif Khan
Yeah. That's awesome. So I just wanted to repeat for everybody, so to get to work with you on testing. it's trudiagnostic.com and it's T R U, right?

Ryan Smith
That's correct.

Kashif Khan
So T R U diagnostics with S.

Ryan Smith
No, just diagnostic singular.

Kashif Khan
Okay.

Ryan Smith
Trudiagnostic.com. And again, you can always reach out to us at support@trudiagnostic.com or email me directly at Ryan@trudiagnostic.com.

Kashif Khan
Perfect. This was incredible, man. I'm sure that you open 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.

Ryan Smith
Yeah, always a pleasure and thanks so much for having me.