Introduction and Ryan Smithu2019s Background

– Welcome to another episode of reversing inflammaging Summit body and mind longevity medicine. And I'm very happy today to invite Ryan Smith, the founder of true diagnostics to join us today.

He's also one of the founders of the pharmacy tailor made compounding, which is become one of the fastest growing companies in the healthcare industry.

Ryan Welcome to the program. – Yeah, thanks for having me Dr. Sideroff, it's great to be here. – Thank you, thank you. Let's get started by uh telling the audience a little bit about yourself and how you got into this field.

– Yeah, certainly. So true diagnostic is a company founded which really is a health data company and laboratory specializing in epigenetic methylation biomarkers and diagnostics. And so that sounds obviously like a mouthful. And so my progression here has been you know, really interesting biochemistry was my undergrad specialty really specializing in peptides and proteins. Then I went to medical school and you know, past my step one but but absolutely hated the clinical portion.

So decided to to leave and do the entrepreneurial thing where we created tailor made compounding which was really a pharmacy that was specializing in this integrative functional medicine space, looking at a lot of novel in inventions.

And one of the things we knew about these novel interventions is they didn't have a lot of data. So we're always looking for ways that we could look at the impacts of some of these really novel interventions.

And really what came up then where these new inventions called these epigenetic clocks. And these were really ways to look at how to say some of the biggest risk factors which is aging from an individual and how some of the things we were using to treat aging um you know in the pharmacy might be able to impact health span and lifespan.

And so I got really fascinated with these clocks so much so that it actually captivated almost my entire attention and decided to to sort of sell the pharmacy in order to get to diagnostic and really jump into the world of epigenetic methylation biomarkers um and really see how we can interpret those new biomarkers in the space of health, but particularly in the space of longevity. – Yeah, that's great.

And as a psychologist, I really appreciate the notion of measurement. When you start doing measurement. You in many respects you really motivate people to pay attention because now they could see the impact of their behavior.

So I really appreciate that approach. Ryan tell me tell us a little bit about your perspective on aging and longevity – Certainly. And I think it it mimics yours a little bit in terms of measuring the process because most people think about aging as defined entirely by one number, which is their chronological age. And unfortunately that is just not a great measurement and I think people know this or should they have been accustomed to to this for several years is everyone knows people that are in their fifties that look like they're 70 and then vice versa, those people who are older and look very, very young. And so this difference is fanatic variation is a good sign to us that we need a better way to measure that process.

Um and and not just I would say a better way, but also to expand on the reasons why it's one of the most important reasons why is aging itself is the biggest risk factor for almost every chronic disease and death, including chronological age.

So if we can improve the measurement, we can also then improve how we treat it or or the things that we can learn

about treatments for this process.

Why Biological Age Matters

And so that's really what captivated me with with this initial introduction. But beyond that, I think um you know, being able to get a lot of wide scale information on how your genes are actually behaving um in the field of longevity and the dysfunction in your genetic expression that occurs with age is re really fascinating.

And so that's really what's grounded me here is is true diagnostic. We've tried to create the best ways to measure that biological aging process through this very unique biomarker. And so I completely agree with you.

Testing is is absolutely necessary. So we can actually uh see change but also then Lauren, what's the best at affecting that change. – Right. So you referred to epigenetic clocks.

Can you explain what an epigenetic clock is and perhaps give us a bit of a history of its development. – Certainly. And this has been a relatively complex topic with a lot of twists and turns over these past couple of years.

Really the first epigenetic clock started in in 2013 by actually another U. C. L. A. Um faculty Steve Horvath. And uh these clocks were looking at this biomarker of epigenetic methylation.

So before I go into those clocks, I really want to define what that is. Um And so epigenetic methylation are basically markers on the DNA. Which are essentially the off switch of D. N. A. By attaching these DNA methylation markers.

You're really silencing a lot of gene transcription. So how these genes go from uh you know being just genetic information to RNA, which is then expressed into peptides and proteins.

Um And so the way that I generally explain this to people who are not in the field is you know, every cell in your body has the exact same DNA. Whether we measured your heart or your skin or your hair, the same DNA sequences found in all those tissues.

But they obviously behave very very differently. Obviously the skin is behaving much differently than the heart. And that's due to this epigenetic regulation what genes are turned off and turned on in each tissue.

And so by measuring these patterns, particularly in blood in 2013 they saw a very strong correlation to someone's chronologically age. So much so that they could actually predict relatively closely, really, within four years, someone's actual chronological age, which was, you know, a very, very big development because this is uh, you know, as I mentioned, we know that aging is such an important factor in people's health.

And this was a way to actually measure it from a diagnostic biomarker perspective in a way that was more accurate than most anything that had it occurred to date.

And at first, this wasn't even used in a healthcare setting. It was used to date, you know, refugees to see if they were adults or minors and then eligible for asylum or they were used, you know, in forensics to see how old someone was if they had DNA at a crime scene. But what they really started to do once they looked at these large scale meta analysis is they saw that people who were older with this testing than their chronological age, um, were at much more increased risk for negative health outcomes and vice versa. Those people who were younger than anticipated with this testing were protected from these negative health outcomes.

What Epigenetic Clocks Measure

And so this was really exciting because not only do we have a method to really now detect aging, but it wasn't just your age, it was also a biological age, one that was associated to these health care outcomes.

And so that was a really big breakthrough um, that we can actually now measure the aging process in a biological manner rather than just a simply chronological one with very, very high accuracy and so in really high links to

disease.

And so this field is advanced and several times over over the last couple of years it's uh these algorithms have become more and more accurate and even today we see new algorithms released almost on a six month basis which continue to improve the field to really increase our resolution of what we're able to find um in terms of these patterns and associations to disease. Um so so now, even though Dr. Corvette had the first generation clocks were already on third generation clocks which are even better and and can even tell you a lot more about your individual aging status.

– So what is the evidence that this methylation process of determining biological age actually relates to longevity? – Certainly. So the way that these algorithms are created are really using computer learning and artificial intelligence.

And so one important point to make is that these are not necessarily causal, we don't know if these patterns are a result of aging or if they're causing the aging process themselves. And that that is one thing that we really hope to solve. But um once these algorithms are created, we always test them to see if they're effective at at predicting aging and disease rates by looking in large cohorts. Things like the Framingham heart study cohort the in Chianti cut study cohort, health and retirement cohort.

And by looking at these, we can sort of prove our hypothesis by measuring the aging rate. Um can we see that people who are at advanced aging are having worse outcomes such as earlier death and more disease and for those people who are younger than their anticipated age, can we have them be protected or live longer and be more disease free?

And the answer is, we we absolutely have proven that. Um and actually, the way that we do that is by hazard ratios. So what is the likelihood of a particular event? And then if you're younger, what is your likelihood versus you know, someone who is the exact same age and vice versa. And with that we see that these hazard ratios, the ability to predict outcomes is better than any other measurement of of biological agent.

This includes things that are relatively well known like telomeres, for instance, which have been measured for a long time but generally aren't that predictive of health care outcomes. Um it even includes other biomarkers, like proteomics or even metabolism, it clocks. And so in terms of all the biomarkers, we can measure, it looks like epigenetic methylation is one of the most promising um for this measurement process and it's proven in those large scale cohorts where we can look at what happened to these patients 50 or 60 years later.

– That's great. It's interesting that it predicts better than uh telomere length. – Yeah, certainly. And actually to expand on this uh we actually can turn these epigenetic methylation information into other surrogate predictors.

So, for instance, we can actually now even predict telomere length just through the DNA methylation measurements. And when we do do that, they have doubled the correlation to age. Um and they're actually more predictive of almost every health care outcome, including time until death, coronary heart disease, et cetera. And so even our surrogate DNA methylation biomarkers can be very, very exciting. And as it relates to this inflammation topic that you are speaking on, we can actually even use DNA methylation to predict different types of inflammatory markers like c reactive protein or aisle six or TNF alpha.

We can actually create surrogate markers just by reading that information. And I think that's what's really exciting is that, you know, some of those earlier clocks, for instance, didn't have a lot of associations, different hallmarks of aging. So, for instance, the Horvath clock originally wasn't related to sell their sin essence for instance.

And but with DNA methylation we can actually predict surrogate markers of all of those hallmarks of aging. So we can look at inflammaging, we can look at cellular senescence, we can look at you know, how proteins are regulator or proteomics dysfunction.

And that's really the larger thesis is that as our ability to read these DNA methylation patterns improves the better that we can get at capturing the entirety of the very very complex aging process. Um And and even create better and better predictors. Um And and not just that but predictors of other disease status is independently of aging.

– So you mentioned measuring inflammation, can you say a little bit more about that? – Yes, certainly. So some some of the original clocks that were trained to predict the chronological age of a patient were really completely disassociated from from the inflammation process. Um And that doesn't really match up because we know how important that those inflammatory markers can be to degradation that we would call this aging process. And so um we know that we needed to expand that definition of aging and do that by by improving the things that we're measuring.

Um And and so uh now we've created by taking both DNA methylation measurements and those inflammatory marker measurements. Um we've been able to create predictors of those in one data set.

Evidence Linking Methylation to Longevity

Um And so right now we can read over, for instance, 100 and 50 different proteins um just from DNA methylation and and I should mention that they're not exactly quite as precise.

They're not gonna meet the gold standard of things like mass spectrometry, but the idea is that with all of this epigenetic data that we can get. Um And maybe even in the future at a very very low cost.

We can read out the functional environment of almost your entire body. So we can predict your risk of multiple different diseases, multiple inflammatory markers, metabolites your gut microbiome all reading the patterns through DNA methylation. And so now even some of the best aging algorithms such as grim age have come out with version two's where some of the first steps in that process is to predict things like c reactive protein um or or hb a one c these these markers that we know are very related to health process and by adding them into this larger biological age consideration, we can get even better predictions of health outcomes.

Um And so so I'm talking I think it's really about two different processes. I don't want to confuse anyone who's listening. One is the this idea of DNA methylation to predict biological age. Um and that is a process that's going to continue to develop. But the way that we continue to develop is by adding more information to that very complex picture.

And to do that, we're creating other ways we can read those DNA methylation patterns to more appropriately capture all of those hallmarks of aging, including inflammatory markers.

So I guess this relates to the fact that you're at the third generation. Um Can you share any more detail about that progression from 1st 2nd and 3rd?

Absolutely. And this is actually one of my favorite topics to talk about right now because I think that if people have had experience with these epigenetic clocks, they might have had in the past, especially in the early days, they might have had some experiences which were not quite optimal.

Um And there have been some initial problems with these clocks which have now been solved. So for instance, one of the biggest issues has always been precision of these clock.

Um uh and and the precision of these clocks have at least originally been very variable. So up to 3.9 years of of of absolute error between a measurement um which means that you're you took it within the course of six months might change by four years and you might not know if that's real aging related change in your body or if it's just noise of the measurement. And so a lot of times these big fluctuations have led people to be disillusioned with the applicability of these.

Um and and and so one of the ways that that has been improved has has been this precision of these clocks has been greatly enhanced over these past few years.

Now. If we test the exact same sample, we usually have less than a 1% variance on that exact same sample. Um so these are now much much more precise and uh and that although that's not necessarily a generational algorithm perspective, it is definitely an important piece of improvement that's happened with these clocks. The

other big improvement has been as we mentioned these generational improvements. So the first generation clocks are defined as clocks that were trained to predict the chronological age of a patient.

And as we've talked about, we already know chronological age is not the best way to measure. And so the better that these clocks got the closer to predicting your actual birthday. If we really wanted to know, we could just ask right, we would need to spend several $100 on testing.

Um And so so the second generation of these clocks switched that paradigm and instead of actually measuring just the chronological age or trying to predict that they tried to predict a constellation of age related biomarkers. So for instance, things like t linear length or vo two max and lung measurements.

Um or even, you know, functional measurements like frailty for instance, and those clocks became much much better and we know they're better because they were predicting disease better than those previous clocks.

Um And this leads to one of the other problems with some of those first generation clocks, which is whenever we applied them to known interventions that beneficially affect aging such as caloric restriction, which has been really well validated in a multitude of animal species. We actually saw that those first generation clocks went up whenever you applied caloric restriction and that doesn't make a lot of sense because we know it so well validated. But those 2nd and 3rd generation clocks, the ones that have been trained on biological phenotype is behaved exactly like we would expect. They actually went down as expected.

And so this is this is important because we don't want people to implement these processes and have the error be so much, they can't find out information or that they're measuring the wrong thing and they're getting the wrong information.

And so we're actually the only commercial company in the market right now that's doing any 2nd and 3rd generation clocks. And particularly the one that we pride ourselves on the most, is a clock that was developed with with Duke and Colombia called the Dunedin pace clock.

And this doesn't output an age, but it outputs an instantaneous pace of aging. And it is by far the most accurate and the most predictive. Um And it's actually the only third generation clock which has been trained on longitudinal samples. So instead of looking at a lot of different patients over a lot of different points in their life, it's actually looked at the same patients across their aging trajectory.

And and that's why it is so highly linked to some of these different healthcare outcomes. And and we're working on some other really exciting things as well.

Inflammation, Hallmarks of Aging, and New Biomarkers

But um but these improvements have made epidemic clocks really actually now applicable on an n of one personalized basis where someone can take this measurement, get an idea of where they're at. Um And then hopefully we can all improve our aging. There's no such thing as too low of a biological age. So we can all try and find what works for us.

Um you know, we both might take Metformin but my epigenetic aging rate might go up and you might go down and so we can get this information on what's actually working for us um to reduce these markers and by reducing these markers, we know that we're also reducing our risk of disease and death.

– Well, the notion of better reliability of of these tests is so important. As you have indicated, you know, you and I are talking about doing some research in looking at the impact of resilience on biological age. And if we do say an eight week intervention before and after measurement, it's a problem if there is great variability in reliability in the in the data that we get. So the better we can get at being precise with a reading and a measurement, the more accurately we can determine whether a intervention makes a difference – Certainly. And and on that topic I would be remiss if while having you on the call in a public setting.

I didn't emphasize the importance of some of those psychological impacts and and things like emotional regulation and stress onto these clocks. Um and and it's been one of the biggest things that I would recommend in terms of treatment intervention is to improve things like your resilience and reduce things like your your psychological stress. I was never a big fan of meditation or mindfulness or some of those other things before this testing, I was always asking myself is, you know, is this mindfulness meditation?

Is this right? But we've seen drastic reductions. And there have been many studies linking resilience and emotional regulation and stress reduction to improvements in these processes. So we might talk about that a little bit later in terms of interventions, but I'd be remiss if uh well, my call with you, I didn't mention that as a point as well.

– Well, I appreciate that actually my next question was going to be in your experience. What are some of the factors that influence biological age? – Yeah, certainly. And this is always a changing topic because as I mentioned, as we improve these algorithms, we're finding different insights.

And so with that being said, there are a few things that we generally see work for everyone to have an improvement. Already mentioned stress and you know, improving that sort of emotional regulation and resiliency, which has a strikingly large effect size. You know, it's uh it's not just that, it's correlated into improvement. It's the if exercise is also very large.

You know, even people who are working on average, you know, 40 hours or more per per week and the stress that is associated with that can on average have a 1.5 year age increase versus those who don't.

And so these these lifestyle impacts and particularly how it affects your psychological status make an important difference. Some of the other things we see work, Almost everyone um are things like caloric restriction, as I already mentioned with some of these newer clocks. And again as I mentioned earlier, caloric restriction is very well validated to improve health span and lifespan in a lot of animals. Um and even in human measurements, like the Calorie study, which was a two-year caloric restriction study where they ate right around 11% less calories than they were consuming or burning per day.

Um Those had really big improvements on all of the ways we can measure biological age, but especially these methylation clocks and we see this again and again again, caloric restriction can make a big impact on reversing these markers.

Um Some of the other supplemental things that we see outside of these epidemiological or diet interventions um are things like vitamin D. Having a major impact um uh and across a lot of different algorithms in different populations. Um Some of these uh studies have shown up to uh you know, 1.8 to 2.5 year age reduction in just 16 weeks with 3000 Iu of vitamin D.

First, Second, and Third Generation Clocks

Um which is, you know, really, really interesting. Um Some other supplemental things like dhe a tends to have a great impact. Um And uh and and so those I would say are really the things we see working in a large majority of people. Um but right now, what we're trying to do is to study some even more, I would say exotic types of interventions, things like Cina lyrics, for instance, things like stem cell therapy or uh you know, plasmapheresis or plasma exchange. So we're getting more information about some of these really novel types of therapeutics that are really exciting.

Um But one of my favorites is also wrap um isn't um rapid mission which has a mechanism of action very similar to caloric restriction and the fact that it's inhibiting m tour um into or one. Um it seems to have a very positive effect on a lot of these markers as well, particularly those newer generation clocks.

Um and I tend to be a little bit uh although there's been a lot of studies out there on things like growth hormone and um and Metformin, I don't know that we see those same associations in our cohort – You're talking about or I know you have uh as part of your toolkit being able to determine rate of biological aging.

Can you explain that and how you're able to get that? – Yeah, certainly. And so that algorithm as I mentioned, the Dunedin paces definitively our favorite. It has the highest precision, the highest hazard ratio predictions of disease. And it responds to interventions we know beneficially affect biology. So it really does everything we really want a biological clock to do. But to create that clock was actually uh you know, initiative that took a long time. It really actually started in 1972 with a cohort in New Zealand um which is why it's named Dan Eden.

It was actually in the town of New Zealand. And this cohort started off with 1000 and 37 Children from the time they were born, it enrolled them into a cohort that tracked their aging process across the lifespan. So over several years, they they sort of measured these functional biomarkers to create a pace of aging for really 21 functional biomarkers, including many of the things I mentioned earlier, things like cholesterol, things like telomere length, um even gum health was assessed and and included into this algorithm. Um and so it's really, really unique cohort that that really hasn't existed anywhere else.

And as part of that cohort, we also added methylation based measurements. And from that we were able to take this rate of aging. We had calculated from their blood based biomarkers into an epigenetic serve yet.

And with that this is how we've seen and validated all of these really great interventions. And so the rate of aging is a more instantaneous type pace of aging. But we see that also increase as we get older. So the idea here is to keep your pace of aging as low as possible for as long as possible, even if you're slightly above a rate of aging of one, which means you're aging more biologically than you are chronologically every year. Um even if you're at one point oh one, you would increase your risk of death over the next seven years by 56% and you increase your risk of chronic disease diagnosis by 54%. And so that can be, you know, major increases. And so that's really our threshold.

We want everyone to keep this as low as possible. Um And you know, if you're one standard deviation above this aging average, you would be considered what we call a fast ager and those in in the validation with the Framingham heart study cohort. Those fast ages were 62% more likely to die than those people who were aging at an average or slow aging.

Right. And so so this definitely impact your risk of disease and your risk of death. But beyond that, I think that some of the most exciting parts of this algorithm have been the correlation to these health span related metrics. These quality of life related metrics sometimes when we were talking about this, uh two patients, people ask, well, why do I want to live longer if my quality of life is so terrible?

I don't want to live in a nursing home. I don't want to have a poor quality of life as I'm aging quicker. And I think that's one of the other things that this study really documented. Um Because we we basically took everyone at age 45. And actually right now uh Terrie Moffitt from Duke University is actually in Dunedin doing the 51 year age follow up of this cohort to create an even another generation of this algorithm.

Um But 50 45 years of age. We also did an analysis and so we looked at things like retinal imaging brain MRI's. We did um you know facial imaging scans and what we saw was really really significant things like grip strength.

As you get older at age 45 as your pace of aging has increased your grip strength and muscle mass decreases. We also see this with functional measurements like your ability to balance the faster your rate of aging at age 45.

The worst you performed on that measure. Staying with actually I. Q. People with who are aging at a rate of of two were on average 15 I. Q. Points lower than those people who are aging at a rate of one. We saw this on the brain MRI's as well with less surface area of the brain less a sort of brain volume.

And in everyone's favor we also saw this with facial aging. And this is a really striking image. If you if you look at the paper you might even see it on our website where we look at all these people across the who are the same chronological age, they're all age 45. But the people on who are the slowest aging members measured by this you needn't pace. Um look maybe 20 or 30 years younger than those people who are the fastest ages. And so I always tell people this is not just about how long you're gonna live, it's about the quality of life that you're living while you're aging. And so that's includes uh you know, you have better muscle mass and strength and the ability to move

about the world the better your aging rate is. But you also think about the world.

Your perceptual reasoning has increased your I. Q. Is increased. Um And then even aesthetically you look better. Um And so I tell people keep doing all the aesthetic things that that you want to keep doing your Botox but also fix the underlying cause of this aging process.

Which is the reason that you're you're looking older on a daily basis. And so um I like to to mention that all those things with the union pays because not only is it the most predictive the most accurate but it also correlates to all of those quality of life metrics which everyone is very interested in.

– Well this is a very fascinating area, particularly the data that you're pointing out because I know when I when we look at stress and the impact of stress, we find that so you talked about a little bit above one and a little bit below one in terms of rate.

Stress, Resilience, and Biological Aging

Well, what we know about with stress is that it's a there's a snowball effect that when there's some impairment because of stress it further, it causes further impairment. For example, There's a mechanism in the hippocampus that is causes a braking system to the stress response. Well, as people have more impact because of their stress, that braking mechanism gets impaired as well.

So it further impairs ability to manage stress. And there's a snowballing effect. And my hunch is what we're looking at here with rate of growth is something similar that you could be just a little bit faster, but there's something that your organism isn't doing optimally that further perpetuates that correct? – I couldn't agree more.

And in the way that I generally explain that to patients as well, that same philosophy is likening it to compound interest, but in reverse right, you always want to keep your money in the banks of the interest or its interest.

But in the case here it's damage makes more damage sometimes. And so it's sort of the opposite of that, that philosophy where you want to keep this as low as possible for as long as possible in order to I think prevent that compounding nature that you mentioned. And to further elaborate on the length of stress and and and these epigenetic age markers. The first Horvath panting Algorithm which is by far the most widely cited in the literature of the 353 places that we look at on the d.

n. A. 85 of those are located at or near glucocorticoids receptor elements which I think you know really emphasizes the impact of stress even more as it relates to that aging process. So so I certainly agree.

I think that you know that rate can can certainly compound if it's negative early in life. – Yeah. Very very interesting. One of the ways that I like to think of this frame, this is that you want your body as as tuned up as possible which means in a place of balance.

And here we're talking about what happens when your body is tuned well versus when it's not tuned well. – Yeah it can completely agree. And I think that you know as these aging definitions continue to expand. You know we uh you know a few years ago we had you know, even fewer hallmarks of aging than we do now.

But I think that the one unifying definition of aging is this progressive loss of function with age. And I think that it goes exactly to what you're mentioning which is uh you know this dis regulation being out of of sort of the home a static set point or where you should be leads to to worse uh dis regulation leading ultimately to worse functioning. – So what is the next step would you say?

Ryan in epigenetic methylation testing? – Yeah so methylation testing is you know if there's one big takeaway from anyone who's listening I think it's it's time to get interested in this testing because this is really where I would say genetics was 30 years ago.

You know we're about to see a massive influx of genetic and epigenetic uh sort of markers for interpretation into a

variety of health diseases. You know that I think that last I checked the genetic market is over 30 billion a year.

But you take the test once in a lifetime. You only take those tests uh once because your D. N. A. Is really stagnant and immutable and and so now what we're looking at is is this epigenetic methylation marks can really bridge that gap.

It can tell us a lot about the functional state of the body particularly in aging for us.

Factors That Influence Biological Age

What we're doing is since our on sort of outset around 2.5 years ago we've really been focused on creating the best in class epigenetic age offering. And to do that we invested a lot into a large research study that we're doing with Harvard to create a multi moment clock. And so as I mentioned, you know aging is very complex topic and we wanted to provide as much information to these epigenetic markers as possible. So we've done um you know, a lot of participants from a bio bank where we've looked at over you know 7000 proteins over 3500 metabolites to get a good idea of all of the different changes that we can see with age and to create the best aging out.

So we're really excited to to launch that and publish on that in the next few weeks even. And so we're really excited about that. We also have some algorithms coming out as I mentioned for sin essence burden to be able to predict in essence.

That's a very hard thing to categorize. But we have a really exciting marker that we've done in collaboration with Ohio State and Yale. To be able to predict in essence burden and some of those other hallmarks of aging with Yale as well. We to have their systems clock to be able to report on aging of unique organ systems all through blood based methylation.

And so there's a lot of developments in epigenetic methylation clocks in age. That will again add resolution to to not only being able to tell you if your aging uh quicker or slower but also to give you a resolution on maybe why.

Now for the first time. And so we're really excited to roll all those things out but beyond that these epigenetic methylation marks can be used in a variety of different ways. Not only can we can tell your biological age, but we can actually even predict when you might die.

We can predict how much you've smoked across an entire lifetime, how much you're currently drinking. We can tell you if you're likely to, if you have diabetes, not just what you have diabetes, but what subtype of diabetes you have where we might be able to recommend um different interventions or we might be able to recommend or I should say project different risks for your individual profile.

So really epic the bridge to this personalized medicine movement that we've seen for a long time where we're actually able to get a really unique signature about you as an individual.

And then interpret that in ways that can really improve your health. And and so it definitely aging has been what has started an aging is a is a massive problem. We continue to hope to to to lead the way on and help fix. But beyond that epigenetic methylation as a biomarker is going to change the way that health care is practiced and we hope to be leading the way there too. – Well, that's great Ryan.

Let me just ask you a question about uh the kind of results that people get when they give you a sample. I imagine you get your biological age. But do you also get the different biomarkers that go into creating that biological age. And so you get, you can see biomarkers that are perhaps really good and then biomarker markers that are needing improvement on.

Do you get sort of like a profile of biomarkers with that biological age? – Certainly. And and we're adding new reports, you know, every 4 to 6 weeks. So we continue to be able to extract more information from this. And I think that's another great thing about our our our platform is that as our information and knowledge of this process grows.

The reports also grow. Um But currently right now we do things like giving you your biological age. We give you your immune age um also with your immune cell subsets. So we can actually tell you your relative percentage of different immune cells in your body like your naive verse exhausted cd four or you're naive and exhausted cd eight T cells. We can even beyond that give you your pace of aging. We also do telomere length, as we mentioned earlier. And as I mentioned, we have some other really exciting age related things coming out like the system's clock age, the death predictor. And this in essence burden predictors.

But we also do other disease related quantification, especially if you're doing this through a physician where we'll do things like your diabetes risk, your 10 year cardiovascular disease risk. We'll be able to do things like how likely are you to lose weight if you implement co workers, some people might lose a lot of weight.

Other people might lose significantly less. And as I mentioned as well we also do things like how much are you currently drinking just to keep you honest and how much have you smoked across an entire lifetime to get an idea of maybe how much damage has been accumulated as a result of that process? We even do things like my topic clock rates to look at the number of stem cell proliferation you're having per year which can be a big risk factor for cancer. And so uh so we'll continue to expand this as as the as time goes along.

Measuring Pace of Aging and Quality of Life

The many people might be familiar with these these things called apologetic risk scores which look at all your genes and predict how likely you are to get a certain type of risk. But one of the really big movements in methylation is to create methylation based risk scores.

So very very similar concept but the idea is that these are are changeable as a result of environment in history and and protocols. And generally these have been shown in actually another study at U. C. L. A. Where we can actually improve prediction over apologetic risk by a substantial amount. And so that is really what's coming is by doing one blood test will be able to give approximate estimations of a lot of other biomarkers but even these functional outputs. So we're also coming out with things like vo, two max prediction, grip strength prediction, walking speed prediction.

And again as these things continue to scale, we'll have more insights, but the cost will remain the same. So the idea is that we'll be able to read out a lot of different value in the future.

But right now that's almost everything you can get on our platform as it currently stands. – That's an unbelievable wealth of information that one can get from that and if they're really working on their health and wanting to improve, it gives them a lot of data to put their teeth into and identify where they need to make their efforts.

So that's tremendous. I wasn't aware that there were so many uh points of data that are available out of that one sample. – Yeah. And it's really incredible that the majority of those things that I mentioned have really happened in the past year and a half to two years, this is still incredibly new. Really exciting.

But the amount of growth that we'll see over the next year, two years or even five years will be substantial. – That's fantastic. And I know you're doing um you're engaged in a number of research studies with a number of universities and and researchers can you give us a heads up on some of the current and newest findings in terms of what does, what you've discovered has an impact.

– Certainly, so, you know, I like to classify this research is into two ways. One is these epidemiological associations. These are all the things that we know in really large cohorts that have an effect. And then there's a separate group that I would call the interventional datasets where we look at an individual and intervention and then an outcome. And unfortunately those interventional data sets are much more limited, especially because You know the way that we measure or interpreting these things change all the time. So some for instance the didn't pays, which is now what I would consider the best measurement only came out in 2021.

So we're still not even, you know, a year and a half away from when it first came out. So again, I think that from an interventional perspective, most of the things that I've talked about already or what we would recommend.

But there's some other surprising findings for instance, like simple Itics we're about to we did a study on the satin corset in with Dr. Edwin Lee from Orlando and found that signal itics don't necessarily have an age reduction effect.

And in fact sometimes they might even increase. You know, some of those aging markers while we still see reductions in the senescence associated secretary phenotype inflammation markers? And so that I think is an interesting study that's coming out here very soon. One of the other things that I think is a really important study which is we're we'll probably be publishing on by um the end of January at least as a pre print. And something that Eric Verdin from the buck institute is also working on at the moment is separating these these biological age signals from changes in immune cell subsets. So as our immune system changes, that's the DNA that we're measuring. And we really need to control for what types of cells were actually testing to make sure that we're not confounded by a different cellular proportion changes. And I know that might be complicated way of just saying the immune system affects matter in terms of how we read these results and whenever we take out those factors of immune cells we get some really strange associations that we didn't see in previous clocks. And so I would say definitely look out for for some of those papers about how the immune system changes can affect the biological aging process. And definitely look out for some papers that that explore things like sin essence um arsenal itics and and how they may not be impacting our health. Like we imagine. – Interesting, very interesting.

So in the last couple of questions here Ryan based on this information, what would you say are some things that the audience could do right now to help reverse or slow their biological age? – Yeah. And this is gonna sound a little self serving, but I would want to highlight that people should get first tested to see where they're at. You know, even if you're not using our platform, there are other platforms out there that you can you can look into um always make sure that those algorithms are published.

Future of Epigenetic Testing and Personalized Reports

So, you know, you're not just going to a fortune teller and you know, make sure they have some data, but but go out there and and see your baseline, it's not always intuitive, some of the some of the world's best athletes that we've measured have extensively higher biological ages, even though you probably wouldn't expect that.

And so it's not always as intuitive as you might imagine. So, establishing a baseline is a great way to actually see what works for you. So that would be my first recommendation. But then beyond that, i from an epidemiological perspective, do the things that you think you probably should do already. You know, one of the great things about this testing is just reinforced a lot of our beliefs and knowledge of behaviors.

Things like mediterranean diets are great, you know, things like beta carotene genes are great for you in terms of aging, stress reduction is great, physical activity is great, but maybe not too much.

And so in addition to that caloric restriction limiting calories um if you have have a physician that you can go to think about having a conversation about some really new and exciting things like rapid mason. Making sure that your D.

H. E. A. Is normalized. Start thinking about even things that might be even more exotic like plasma apheresis um um or you know diluting your plasma by giving blood.

Those are all things we see work almost in everybody. And really I would say at the moment relatively low risk strategies which could have a really long term effect. – So you mentioned reducing caloric intake but do you have data on uh intermittent fasting? – So we don't have a controlled study unfortunately. But with that being said we do ask almost every participant who takes our test about their dietary behaviors.

And so we do have a cohort is more like an epidemiological study and we don't necessarily see that intermittent fasting improves the biological ages. Unless it's also included with caloric restriction.

So I think that if you're eating the same amount of calories in a day no matter when you eat them. I think that we don't necessarily see an effect. But if you are reducing calories we we certainly do. – Very interesting. And finally how can people reach you?

Ryan they want to get some more information. More information about your products. – Yeah so it is a fast growing area and so we love to distribute information knowledge and so if anyone would like to reach out to us, they can reach out on our website at TruDiagnsotic.com and they can reach out to support at true diagnostic or Ryan@trudiagnostic if you have any questions we love to answer and share data whatever we can at the moment um and hopefully we'll be doing another sort of ask me anything with you Dr. Sideroff in the future and so hopefully people can tune into some of those things as well.

– Thank you so much. And yes we certainly will stay in touch because again measurement is so important wherever anybody is in their lives getting the baseline so that they know whatever they do subsequently what the actual impact is always very important. So I think it's a very important service that you're offering. So thank you and thank you for your time today.

This has been a fascinating conversation Ryan, thank you. – Yeah thanks so much for having me and look forward to sharing more updates as they come – And to and for you and I to engage in that research.

So we have more intervention data – Certainly I think that we're excited to run that through and hopefully it should be a quick and easy project. – Very good thank you