# 093 - humanOS Radio - Hannah Went - Measuring Biological Age Transcript

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## Introduction to epigenetics and health measurement

I truly think epigenetics is causing a paradigm shift, not just in the laboratory testing space. I would go as far to say the entire medical field as a whole.

Human OS. Learn. Master. Achieve. Measuring health is big business. There are literally thousands of tests to measure some aspect of your health. And it's something many people value and spend money on.

We wanna know our health status and whether some intervention we are dedicated to, whether it's something lifestyle-based or even compliance with the medication is working and worth the money and effort.

This is the promise of health measurements. The global biomarker market was valued at $59 billion in 2023 and is projected to grow 12% year over year to a market size of $104 billion by 2028. So, the biomarker business is big.

What exactly is a biomarken? Simply put, a bio marker is any characteristic of the body that can be measured and used to assess health and functioning.

A biomarquer that is used identify the presence or absence of a disease is more specifically a diagnostic. Today I get to speak with Hannah Wendt, co-founder of True Diagnostic, A health measurement company that was founded in the year 2020. One of the reasons I'm keen to speak with Hannah is because they are at the forefront of research in this field since they began.

I see them as a product company, but also a research organization that is responsible for pushing the field forward. The company is involved in over 30 clinical trials with prestigious academic institutions from around the globe in one way or another, exploring ways methylation status and changes associate with disease outcomes, longevity, and even the impact of interventions that hope to positively influence how we age.

Under her leadership, True Diagnostic has developed one of the largest private epigenetic health databases globally, which includes data from over 35,000 patients.

Additionally, Hannah created Everything Epigenetics, a platform where she shares insights on how DNA regulation impacts health. Her work and contributions to the field have made her a respected voice in discussions around biological age and the potential for its reversal or deceleration.

So Hannah, welcome to the show. I'm really glad to have the opportunity to speak with you today. Yeah. Thank you, Dan, for that wonderful introduction.

And I am excited to chat with the you and have your listeners hear all things about epigenetics as well. So let's start here. What is the concept of biological age?

Yeah, it's a great starting point. So the concept of biological age refers to how old a person seems based on more their physiological functioning of their body rather than their chronological age, which is simply put just the number of years since you were born.

## Defining biological age

It only increases. Whereas this concept of biological age is determined by assessing various biomarkers that reflect the true health and functionality of various organs and systems.

And think of that as being bi-directional. You can increase that, or you can decrease that. Or you keep it steady throughout a period of time as well.

how are you aging due to your environment, your behavior, rather than just that chronological-based age? Think, you know, for a second, picture in your mind a group of three people who are all 45 years old.

All right, when you picture that, I don't know exactly what you see. I do not see one standard face, right? Because I know some people, who were 45-years-old, can look much older, and then some that can looks much younger as well.

And that's why chronological age really isn't a good biomarker to predict other outcomes. Thus, we're aging at some other level, and that is really what that biological age is capturing.

What are some limitations of this concept in general? Oh yeah, there are a lot of limitations I would say, a list of of the limitations that we can go through depending on how you actually view this concept.

Variability within the biomarkers, There's no single set of biomarks that universally defines biological aging. And I think that goes back to what even is aging, what's biological ageing.

There are lot different theories of how we're actually aging I actually went to the first inaugural Biomarkers of Aging Consortium at the Buck Institute out in San Francisco last year, and I think they'll continue to have this conference every year which brings together researchers in this space and people from companies like mine, True Diagnostic, who are trying to capture this process in a specific pathway.

And they're bringing in medical doctors as well, so healthcare providers that are actually using these biomarkers in clinics. I would say the number one limitation is what does this really mean?

What are we capturing? Where are reversing or de-accelerating to an extent? And what is that mean for the future of our health? Morgan Levine of Yale describes biological age as a latent concept similar to IQ.

With latent concepts, you cannot measure them directly, but you can infer their value based on other things that you CAN directly measure. In this case, biological age becomes a global score, if you will.

That is, quantifying the different inputs into a value that theoretically represents one's biological Understanding that helped me understand that this isn't something that we can find in one particular point in the body or even say that is the source of biological aging.

So for listeners, that's an important point to understand as we continue this discussion. But still, even if we cannot measure it directly, it can still be of great value.

as it becomes increasingly predictive of things we care about, like disease mortality functioning. So what are some ways that researchers have looked to calculate biological age?

Anyone can create a biological age clock where you can enter a certain metric into a formula and get a number. You then need to validate that number, understand how it was trained.

But on the flip side, some biological-age concepts that we may be very familiar with are things that could include telomere length, DNA methylation patterns used in epigenetic clocks.

There's different levels of various hormones you can use, even cardiovascular health or cognitive functioning and more. So there's this wide array of biological ages we can capture that may be a more accurate or precise picture of someone's individual health status and potential longevity compared to that chronological age number.

Yeah, I found that really interesting as I was looking into this subject and learning more about it, that there are many, many different ways to try to create a predictive model that is assessing this theoretical concept of biological age.

## Validating biological age clocks

In fact, my last podcast was with Vankash Kapahee from the Buck Institute where we talked about eye age, which was a collaboration that he did with Google, where they were looking at the fundus of the eye to a biological age score, which was really exciting to me because imagine in the future you could go to, let's say, your ophthalmologist and they would do a fund-a-scan and be able to give you a fairly accurate picture.

So yeah, there's lots of different ways to do that. Generally, what would you want to see in any model that was designed to predict biological aging? How would validate that?

What's the general process like there? When I get Google alerts that have new biological age clocks created or these interventional trials and sheets, I will ask myself these five questions.

And if they don't meet any of those, i may not read the paper in depth. I may scan it. It's just not going to be as interesting to me personally. Number one, is it published in a peer-reviewed journal?

And is predictive of all-cause mortality and morbidity? That, I think, is really the number one factor. And I know it sounds silly, not all of these biological age clocks are going to be published in great journals.

You need to have some knowledge about how papers are published and the review process to really be able to analyze them properly. And then is it predictive of death and disease outcomes?

Those two go hand in hand because if it's published, you're going to be able to tell if its predictive about those health outcomes. So that's number one.

Number two, does it correlate with quality of life outcomes and not only lifespan, how long you are living. on this earth, but essentially health span.

So does it correlate with things like brain imaging, for example? Does it correlated with thing like facial aging or functional movements as well? Those are all very important.

Number three, is it precise? If they're accurate, it's getting closer and closer to something that's known, like your chronological age, right? So these clocks instead you want to ask, are they precise and where is the reproducibility data within those actual clocks?

Hannah, let me interject here real quickly. As I mentioned in the introduction, there are thousands of health tests and not all of them have undergone the same standards of validation.

It's a huge endeavor to validate a test that takes a lot of time. And if you're trying to figure out how accurate your test is, you typically see how well it lines up with a current gold standard.

But these new tests are entering into new grounds, so there might not be a gold-standard to compare to. So I appreciate your emphasis on precision, where the results are consistent if your were to sample the same person repeatedly in a day.

That's got to be both challenging but a fascinating part of this field. Well, I think if I can just reply there again, one important thing to note is we're a CLIA certified lab, which is a fancy way of saying we check all the rules and regulations in order to even properly run this testing at our facility in Lexington, Kentucky.

Traditional laboratories, like if you're going to get your blood drawn for a hormone panel, CBC, et cetera, and go to LabCorp and Quest, they're gonna be CLia certified too.

But according to CLIAA, you can have up to a 20% variance. in your blood-based values, which is insane. I didn't know this until recently. That goes back to the fact that we need internal data.

We're measuring internally how precise these markers really are. But even for your standard lab values I know health care providers who will send samples at the same time to different facilities and to same facility even, but get

vastly different numbers.

So yeah, it's pretty fascinating. Yeah, that 20% variance is enough to be either categorized as healthy or be put on a medication. So that's a big deal.

You were going to say a fourth point and then I briefly interrupted. This is great conversation. There's two more. Number four is, do these markers actually respond to interventions that beneficially affect the aging process or the biology of aging?

And what I mean by that is these clocks need to able to respond, but not too much. So they need to change with things like caloric restriction, which have been proven out in animal models to slow down aging.

Even things, like synolytic therapy as well, things that we actively know should benefit our underlying biology. And then the last one is going to be, does it explain why you're aging?

Does it give you feedback? And this was one of the limitations previously is a lot of these biological age clocks, they just give a number and you kind of look at it and go, I'm older, younger, great.

That's that. But now how we're creating these new kind of biological age clocks, we know the components or the factors which may be driving that aging.

Thus we can actually tell you exactly what you need to target. So you want to see peer-reviewed. If you want to see that a particular test is being used by researchers so that you have replication and adoption, people in the field find your assessment compelling to be using it in their protocols, which require a tremendous amount of effort to get approved.

That always gives me more confidence when I'm looking at any sort of biomarker test that's out there. Has that hard work, expensive work time-consuming work been done?

## Genetics vs epigenetics

We talked about now, biological age can be looked at many different ways. There's not just one way to do it. What are the leading ways that are currently considered to be gold standard or best practice to assess biological aging?

the gold standard is by far gonna be looking at the DNA methylation or epigenetic interpretation. And we can talk about that further in depth here soon.

More people may be familiar with a older golden standard, which was telomere length testing at one time. The only reason I bring that up is because what we realize now in terms of biological aging is that telomer length only makes up about 2% of our entire aging variants.

Whereas when we're looking at epigenetics and DNA methylation, we are even starting to see upwards of like 80% in terms of all of health outcomes. Don't get me wrong, 82% is better than 80%, but we don't want to solely focus on the telomeres anymore.

So I do think epi genetics is the leading way at this time and continues to prove out to be the best way biological age is measured. So Hannah, if you wouldn't mind, please give our audience a primer on the differences between genetics and epigenetics.

Yeah, absolutely. So genetics is your hardware. You're getting your genes, your nucleotide sequences, 50% from mom, and 50 percent from dad. And those are never going to change.

They're going be the same in every single cell type. It's the nature makeup of your body. where with epigenetics, epi is a Greek prefix, it quite literally just means above or on top of, we're looking on the top the genome, and I call that the software.

So your genetics is the hardware, but the epigeonetics is really controlling that hardware that genetics. And for epigeneetics it's going to be different in almost every single cell type.

Your genes, your genetics is the same in an eye cell and in a heart cell, but why is your eye your eyes and why's your heart your hearts if your genes are the thesame?

And it's actually because of your epigenetics, the expression of those genes. That's how I like to compare the two. There are a lot of other ways you can compare differences.

Main point being too, you're genetics aren't going to be changing. Your epi genetics are going be modifiable. You can actually start to retest your Epi Genetics and it is that nurture component.

It's how is everything you're doing actually affecting you at the epigenomic level? Again, it's about 80% even higher of our health outcomes, where genomics is around 20%. I like that analogy of hardware and software.

Hardware is your genes. Epigenetics sits above your jeans and controls whether this genetic sequence is signaling for the creation of an eye cell or a heart cell.

On top of that, it's also something that is influenced by lifestyle, environment, your experiences. As such, epigenetics will change over your life, and this is what is going to determine what genes are expressed and which ones aren't.

And we can measure this. So that's our primer on the difference between genetics and epi-genetics. We are interested, of course, in measuring epigeneetics now as the gold standard for biological age.

Let's now talk about the various ways in which epigenetic tests can be performed. How are these biological samples collected, for instance? These samples can be collected in all sorts of different ways.

You'll see companies offering a blood test or a saliva test, or even urine. There may be a couple other collection processes you can go through as well.

I recommend using one that is just going to be blood or blood spot card.

## How epigenetic tests are collected

The reason being is because all of these algorithms, like we went to the first point, that are published in peer-reviewed, noteworthy journals are going be created using blood as that tissue type.

Secondarily, we want to use blood as a sample type because again we wanna be able to relate this to outcomes. How predictive is it of all-cause mortality and morbidity?

And we only have blood biobanks, right? We don't have saliva biobic, so we can't follow people across their entire life with DNA from their actual saliva.

If someone is listening and you know of a saliva biobank, I would love to know where that is located and how we can work with them because that would also make for ease of use.

But it is just a simple fingerprint blood spot card. Blood spot cards, if people aren't familiar with that, is that different than getting a blood test?

Yeah, absolutely. Super easy. You're just pricking your finger with a couple of lancets, maybe even just one. Then with just probably the size of a quarter, you fill on a little card and you bandage your fingers up and ship that sample back to the lab.

And you'll get results in about two to three weeks, where as if you're getting your larger blood drawn, as we call it,

You'll go out to Quest or LabCorp and have someone take a few tubes of blood.

So this you can actually do in the comfort of your own home. That does sound a lot more convenient and accessible. Tell us about the evolution of these tests, where it started and where we're at now with the field.

These clocks have now been around for a little over 10 years. And you hear people say biological age clock and epigenetic clock. What we mean by clock is we're just taking a group of those DNA methylation epi-genetic markers and using machine learning to inform us of how predictive we can be of some type of outcome.

So we are using Machine Learning AI to create a model. That's what that clock really is entailing. Ten years ago, I wasn't at the conference where Dr.

Steve Horvath, who pioneered this field, will probably win a Nobel Prize for his work, where he presented that if we look at DNA methylation, it can actually predict chronological age.

I was there, but I know people who were, and they said that their jaws dropped to the floor because in science you just don't see that correlation. So it's really cool science, right?

Those are called first-generation clock stand, meaning, again, you take a sample, look at the DNA methylation, and we guess your chronological age. That's good for things like forensics to see how old DNA sample is at a crime scene, to how see old refugees are, see if they can seek asylum.

So there are use case scenarios for those. And at one point, that is what you would get from these testing companies. Recently, we've made a lot of improvements where we can capture second generation biological age.

And this is where use other underlying data. So think clinical lab values, metabolites, proteins, think physical functions, even telomere length. We're measuring all of that data and using that in the creation of the DNA methylation algorithm or CLOCK to predict something that is truly biological.

So, really, we only want to use second-generation clocks moving forward.

## From first-generation clocks to multiomics

I love this story from the first- generation clock era. Dr. Gregory Hanham, who then went on to create the Hanoum clock, did so serendipitously. He discovered that there was this pesky covariant in his research where his samples kept tracking with age, and he brought this up in a lab meeting on how to resolved this issue, but the lab paused and said, wow, that's actually really interesting.

So correlating with age is interesting, it isn't exactly what we care about when we're trying to understand biological age, which could differ from chronological age.

The second generation clocks detect biological better than the first generation, correct? That's absolutely correct. I love that you brought up Dr. Gregory Hannem as well.

He doesn't get enough limelight as Dr Steve Horvath does, so I appreciate that. You brought him up too. Yeah, definitely. So we talked about some of the limitations of biological age as a concept.

It's like IQ, it's a latent variable, you can't measure it directly. What are some limitations? Of these epigenetic assessments of Biological Age? We're still figuring out what they mean.

You could go back to the limitations that I mentioned, right? Do the clocks actually meet this criteria? There's just not a universal way to interpret this data, to control QAQC laboratory process downstream.

One thing that's very exciting, Dan, that might want to mention too is we use Illumina to process all of our samples in the lab. For those who don't know Illumina, they are a very large company and have run about 96% of the entire

world's genomes, but they basically create the infrastructure, the machinery we can run the samples on to look at DNA methylation.

DNA methylation in epigenetics is so new, we're learning so much about it, that they actually don' t know how to interpret that data. And that's a really big flaw, is that we read the data but we don t how interpret it.

We're actually creating a DNA Methylation Software Analysis Suite at True Diagnostic. which will be able to be given to other labs and help streamline that process of interpretation, I think that's a really good start there in terms of solving the limitations into how we actually read this data.

But I there has to some type of cohesion, some kind of agreement, that way we can start using this in medical practice, saying follow this regimen or this protocol or try this strategy to start to see changes in this.

thus starting to see reversal in all of those age-related diseases and even death. We mentioned the hallmarks of aging already. Again, these are not necessarily why we age, but they do reliably occur when we aged.

Do we know if epigenetic measurement is capturing all aspects of these hallmark? Yeah, great question. Definitely not all of them, unfortunately. So there's definitely incomplete coverage of the aging hallmarks there.

These aging Hallmarks keep expanding as time goes on. I won't be surprised in a couple of years if we get a few more. Like you mentioned, some of these hallmark of aging include genomic instability, telomere attrition, epigenetic alterations, phosphoproteostasis, dysregulated nutrient sensing, et cetera, and most biological age tests are only going to be focusing on one or a like the DNA methylation or like telomere length?

Maybe the more important question to start thinking about is how is epigenetics in general actually associated with some of those hallmarks of aging, right?

Can we report out other hall marks of ageing through the lens of epi genetics? The testing itself, they're not capturing the entire aging process, we're very transparent about that.

Or even all of the underlying mechanisms contributing to aging as an individual. But if we end up with a method to be able to capture components of aging, so epigenetics seem to able capture things like nutrient sensing, stem cell exhaustion, mitochondrial activity, which are hallmarks of ageing, and not as well other hallmark, at least capturing some is valuable, but incomplete.

And so this new idea of multi-omics tests is something that you're taking advantage of. Tell us what you are doing with multiomics. When True Diagnostic was founded back in 2020, we set out on one mission.

We had just one goal, which was to create the best scientific algorithm, or again, clock, that still analyzes epigenetic patterns to accurately quantify that biological aging.

But we realized this needs to be a second generation clock. It can't just be first generation clocks. So we need an extensive amount of data. And there's no better place to go than a biobank for this.

So we actually partnered with researchers from Harvard University and their partners, Biobanks. They have a lot of great longitudinal outcome data over the last 50 years.

And we were able to collect data from that multi-o, and by multi I mean interconnected bio data. layer your epigenomics. Remember, your hardware, it's not going to change, but then your Epigenome mix is actually controlling the expression of those genes.

You have your transcriptomics, which is going be your messenger RNA. It's going talk to your proteins. Your proteins are going fold and give off certain metabolites.

Metabolite is gonna be another layer. And you get that end result of your phenome, or your pheno mix, so your

Phenotypic Outwards Expression levels and what that actually looks like.

So that process took a long time. It took about three and a half years to finalize. But last October, we launched what we think is the best biological age clock ever created.

And that's our omic MH algorithm, named after that idea of the multiome. In particular, the layers we included in that were clinical lab values, metabolomics and proteomics as well to really drive that clot creation.

There's nothing that says a biological age test needs to focus in on only one type of measurement. They could take data sources from anywhere to say this is the most predictive algorithm and that's what these tests seem to be doing.

So first you have to able to capture all that data. Now you've AI where you can, you now have the ability to create insights and meaning out of massive data pools, so this is all great advancements.

Let's talk about aging pace. Aging pace is different than true age score. Tell us about what aging is.

## Aging pace and intervention tracking

Yeah, so the 18-PACE, I didn't mention this kind of technique in order to create these clocks, but we would technically call this a third-generation clock.

So a 3rd generation clock is really using longitudinal data from the same cohort across a time point. This is also called the Dunedin PACE algorithm. If you're familiar, it's a study that happened out of Dunedin, New Zealand, where they followed about a thousand individuals starting in 1972 and 1973, and they're still studying them today.

It's. A really unique study, one of a kind. I don't know any other longitudinal cohorts that have a 96% retention rate. So what they did is they captured biomarkers, DNA methylation, epigenetics, and created this third generation clock that isn't giving you an age, like a biological age number, but it's a pace.

It's like speedometer. So how quickly are you aging biologically for every one chronological year? And if it's faster than one, over time, you're going to see your biological age clock increase.

And, if its slower than 1, great. Over time you are actually going decrease that larger biological. So, this is really, really good for end of one precision based medicine to give you quicker feedback because it is quite literally telling you like a 3 to 6 month running average of what's going on.

In a talk I gave at the Institute for Human Machine Cognition on how to measure health, I depicted a scenario where a 50-year-old man got a biological age test and it had him at 52, so two years older than his chronological age.

But he also got an aging pace measurement that is separate from his biological-age score, and that had an ageing at 10 months for every year. This individual was doing shift work in their 20s and living a harder lifestyle and aging faster.

And because of that, he quantifies as being two years older than what his chronological age is. If he just got that measurement, He might think my health efforts are not really paying off because I'm older.

But actually, his aging pace score says that he's currently doing things right. So that's super valuable. These are two different tests with two types of value.

It's good to look at them both separately. We offer two products. The first product is this complete kit. You're getting the omic-m-age I mentioned, you're giving the pace, how much you've smoked across your entire lifetime, and how you consumed alcohol and other aging scores.

I recommend people do that one at baseline. It's important to really capture everything. If you can, you want to do it probably every 9 to 12 months or so, but that one is also going to cost the most as well.

So it's going be around $4.99. The other product we offer is going one people can use for a smaller retest window. It's called the TrueAge Pace. Paced hinting at that it includes a Dunedin paste in our interpretation.

of telomere length through DNA methylation and epigenetics that may give you certain hints into your senescent cell burden. And that's how we really like to interpret it.

That's going to be $229. So there is a pretty large cost difference there. You can do that one as frequent as every two to three months to get more feedback on, hey, is what I'm doing working?

Is it not? Do I maybe need to adjust a certain regimen here or there? We may actually see a large infrastructure change from Illumina before the end of the year.

So I do imagine these prices going down. Yeah, that's terrific. You can do these tests more frequently without a cost burden getting in the way. And the more data that you have in yourself, the better.

In the future, AI could be looking back on your historical data. The more that it's there, then more you're able to potentially find insights that might benefit you and change your trajectory going forward.

That's great. So, ideally, with this true age complete, you're going to get your biological age, and you are also going get you aging pace. You can do this once, every 12 months or two years, but it's a longer time interval.

Then, on an ongoing basis, every three to six months or so, you could do an aging pace measurement, if you're keen on looking at these things frequently, to capture a narrower window of time to see how you are doing recently, similar to how hemoglobin A1C captures average blood glucose over a three-month period.

So, for aging-pace, how much time is it capturing? Is it a 3- or 6- month window? Yeah, I would say in between three to six months. I don't think we can tell exactly.

Um, we do know it can change in as little as eight weeks, especially if you're changing things like diet. We just did the twins diet study. It was in the, you are what you eat documentary on Netflix, looking at vegan versus omnivore diets and twin pairs.

And we even saw the triage pace change over that eight week period too. What diet seemed to do better with… Yeah, vegan. Vegan actually did better, with some symphony-age interpretations.

So individual organ systems were slowed down. We weren't controlling for everything. People on the omnivore diet were eating more calories. They weren' t on a healthy omnibore-diet, if you will.

The study was designed for that specific purpose, but I think a lot of people interpreted it as flaws of the study. What I thought was really interesting though is when you dive in to even the individual components of the omic MH, we could see individual metabolomic and proteomic-based changes that are aligned with previous research when it comes to vegan and omnibore diets.

So many of those comparisons studies come down to calories. I'm glad that you mentioned that. But you have to acknowledge that some diets might be easier to consume a calorie neutral or slight calorie deficit diet.

So if they're controlled for calories, maybe you'd see less of a difference or even opposite results, possibly, but you have to acknowledge that some diets are easier to overconsume.

I have keep that in mind. On that note, we have something that can assess our biological age and the pace at which we're aging. We talked about diet, what else is being looked at to influence the results here?

## Lifestyle factors, supplements, and clinical trials

We're going to go with lifestyle factors and stick on those for a minute or two. Stress, sleep, and physical activity are huge, right? They're massive.

Those are the big four if you add the diet back on top of it. Again, rather intuitive. I think we see massive changes just in those lifestyle factor alone.

That's why we have lifestyle health care providers. It's by we had integrated functional providers who are counseling us on how to live a healthy lifestyle because it's easier said than done.

I think that speaks volumes even though it may not be as exciting to talk about. The biggest areas of opportunity for people interested in their health is what I call the fundamentals versus exciting new molecules that we think might intervene in our physiology in a way that does influence these.

But we overlook stuff that is mundane but highly meaningful because we've heard it so many times. But are we actually implementing? the standards of guidance in our life and changing our pattern of living can be quite challenging.

But it's good to see that. For example, the diabetes prevention program, where they were looking at people that were pre-diabetes and their incidence of developing diabetes over a three-year period, they had them either on Metformin or a lifestyle program.

MetFormin reduced the incidence diabetes occurring after three years by 31%. That's amazing. Lifestyle was close to 60%. So pretty much double what you see with these meds.

Gotta keep that in mind. If we think about those fundamentals and the mechanism of action by which they follow, take caloric restriction, for example, you're thinking mTOR inhibition, right?

What can actually slow the growth down? When we get into compounds from a supplement standpoint, we see broccoli extract following almost a mechanism action that's going to help reduce inflammation, oxidative stress downstream as well, especially if you are someone who has a lot of oxidated stress already.

there's kind of that antioxidant push and pull, if you will, where we don't want too many, but for those people who do qualify, there could be a nice stack you can create there.

On top of talking about the end-to-end inhibition is, of course, rapamycin. I just went to a longevity conference mastermind in New York this past weekend, and rapamysin was definitely a massive Subject to there, but I think at the end of the day, we all agreed this has not been studied in humans, right?

Which makes the push even further for these aging clocks. How do you actually measure the efficacy of these? Especially when they're probably not ever going to go through the FDA approval route.

So there's some clinical trials that we're pushing through here at True Diagnostic, one of them including rapamycin, so we can understand how does this affect the epigenome, longevity, lifespan, and health span too.

The field itself is just really underfunded, right? The TAME trial was initiated, it was either like nine or 15 years ago. And guess what? We haven't done anything with it.

That's a trial looking at metformin and how it affects aging. So that goes without saying that we need more people involved. We need standardized large cohort datasets.

And sure, something can actually work at the general population level when you're testing it, especially with these compounds. But what it's going to come down to at end of the day is your actual epigenetic makeup.

Just because everything you are doing is affecting your epigene makeup, it is not going be the same as the person in the study. Even if we agree that we are not changing anything, our environment As a silly example, if we have plants in our house compared to someone else who's in the study who doesn't have plans, it's been shown there's correlation with more green space reducing epigenetics, right?

There are always going to be other factors which may not even be truly considered in that study design or makeup. So an argument or criticism of epigeneric clocks has been that they're oversensitive to inflammation.

We know that. acute inflammation response to exercise happens. Have you done any standardization work to see if a person has, let's say, done a hard workout the day before, they take your complete test, might that alter the results that they get?

So, you know, lets say they took it again a week later, or they haven't aged considerably, but do they a different score? I don't believe that would be a true concern.

People who say, oh, I consumed a lot of alcohol the night before, would it actually affect my biological AD score, right? Obviously, it's going to have different markers compared to the inflammation that you're getting from the exercise.

But I think it has been accounted for when you are actually looking at the single kind of probe analysis that makes up these bee chips on what we actually run the sample on.

There's a lot of QAQC that goes into it. But then additionally, the algorithms are going to account for a of that noise. So it's not like when we read those methylation markers, we're scanning through them once and saying, awesome, let's put it in the algorithm and get the score.

You actually get a replication and we are scanning your sample almost five times. And it is just not going pick up on those faster paced changes to lifestyle It has to be habitual.

We've seen that in several internal studies as well. So this is a really fast moving field. We've gone from more singular measurements with just epigenetics to multiomics.

Your own algorithm for these tests is regularly updated. I kind of see this like a SAS product, you know, where you buy a product you're paying a subscription and you are getting the latest addition.

So, if you make changes to the algorithm and a person has already received one of their tests, say a year ago, is that old test updated with the new algorithm.

Absolutely. We're about to release our new Symphony Age with Yale at the age of 11 different organ systems in a month or so.

## Future of epigenetic biomarkers

So literally the first person who took true diagnostic tests back in 2020 can say, hey, I want that report, take my raw data file and read it through this algorithm or through the lens.

I would also argue that data is four years old. You need a new test altogether. And we should probably update that anyways, but you're exactly right. It really is like a SAS product where we can start to update you.

That's why it's so important to us to actually measure as many methylation positions as possible on the array. We measure about 1.2 million. Some other companies may just measure like 10,000 or 100,00 which is still great, but to us it allows the expansiveness of reading previous reports in the framework of the question you just asked.

You just mentioned symphony age, where you're looking at different organ systems and how they might be aging differently. So a heart could be a different age calculation than your brain or a kidney.

Is this a separate test or is this an upgrade to your algorithm that will be included in your true age complete test? Yeah, it'll be an included on top of everything else that we're including.

And so it will one that would be there moving forward and then anyone who's taken it previously can upgrade their report too. Okay. Last question, so of your future forecasting, where do you think this field might be in like three to five years?

With the additional work we're starting to do with Harvard with epigenetic biomarker proxies, interpreting other data markers, other points just through this blood sample, just though this price point and it's going to continue to get cheaper, we can report out over 4,000 clinical lab values, metabolites, and proteins with a one-to-one ratio about.

It's not going be perfect, but our correlation value is about 0.98. We can now get a tremendous amount of data on ourselves and this turns out to be its own type of clinical or consumer challenge.

So either challenge for the doctor, challenge with the patient. Many of these biomarkers we might be unfamiliar with and how is a practitioner thought to use this information in their clinical practice?

Is some of it just informational and some it is meant to actionable? Yeah, the biological aging is definitely additional to what they're already doing, but they should be measuring it.

They want to attack that number one risk factor for all cause of mortality, morbidity. But I think you're asking particularly about these epigenetic biomarker proxies in the future.

And for those, again, it's not going to act as a replacement right away. We're going have to do some accuracy testing there, right? But eventually that's the goal that it is going be a replace.

I truly think epigenex is causing a paradigm shift, not just in. The laboratory testing space, I would go as far to say the entire medical field as whole.

Great. Well, Hannah, thank you. Very impressive to see what your company has been able to accomplish under your leadership. For me, being able reliably capture a global health measurement like biological age is trying to do is valuable in many ways.

It can help test interventions. It could help individuals understand how their efforts are paying off. We already know a lot of ways about how to be healthy, but we don't know everything.

And this type of test can add meaningfully to move the field forward. So thank you for your work, and thank for coming onto the show and chatting with me.

Yeah. Thanks, Dan. I super-preciate your time and look forward to catching up soon. any.