Introduction and Guest Background

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So that would include, you know, everything from, you know, cancer to cardiovascular disease to Alzheimer's. We now are able to predict your five and ten year risk of all of those diseases with the same blood spot.

Now that we used to do biological age, and the amount of data that we can get from this is just really incredible. This is doctor talks, real talk from real doctors on the issues that matter to you most.

I am super excited about this particular interview today. This is the incomparable Ryan Smith. He I've been a massive fan of yours, Ryan, for a number of years.

Going back to your days. It's a tailor made. You a brilliant mind. And I'm very honored to have you here on our podcast. Look forward to this conversation today.

This is the every young podcast. I'm, Rich Hanley. And, I'm very lucky to be here, in the room with you. Let's get started. Yeah. Thanks so much for having me, I appreciate it.

Awesome. So let's let's start with a bit of a biography. How did you get your your start in this space? And let's go back to the beginning. Yeah. It's been a long and winding road, so I'll try and abbreviated as much as possible.

But, you know, I was a biochemistry undergrad, did a lot of specialty work and peptide and protein synthesis. So peptides and proteins were always, I would say pretty exciting for me.

But I always wanted to go to medical school. So I went to, the University of Kentucky, really after undergrad, and went through my first two years there, where I was doing most of the clinical work, right.

Learning about all of, all the things you need to learn in medical school. But then in the third year, going into the clinical portion, I just sort of hated it.

And so, I've made that that point. What I always say is the very stupid financial decision to, to sort of quit halfway with a bunch of student debt to do the entrepreneur thing instead.

And so, given my background with particularly proteins and peptides, we created a compounding pharmacy called Tailor Made. Compounding that, really specialize in bringing a lot of the peptides that everyone knows today into the market.

We were the first to launch things like BPC, you know, most of the additional growth hormone secreted cogs like the CJC or the Upper Moreland. We even brought a lot of things that are now FDA approved medications to the market, like PD 141 and, a few other things.

And so that was a really great experience. For me, you know, it was my first time, you know, sort of running and managing a business. And it grew incredibly rapidly.

We're the fourth fastest growing company in health care, mainly because these cocktails were hitting a really, I think, big market need, they were really helping people, in a lot of different areas.

And as I mentioned, there we were sometimes we were just early in their clinical approval process. So we, we, we

grew to, you know, over 220 people within two years of business.

It was massive growth. But, unfortunately, those days sort of came to an end with some of the peptide regulations that happened. But, you know, one of the whole things that we were sort of servicing at that time were physicians who were really treating aging as a primary mechanism.

From Medicine to Tailor Made and Epigenetics

And so I'd always been interested in this because I knew that one day the FDA would ask about all the things that we're doing. And I wanted to have data, but I didn't have time to do a 40 year, placebo controlled follow up on all of the things that we were doing.

So I was really looking for surrogate markers. And that search really led me to this idea of epigenetic methylation and biological age. Started to learn a little bit about this, and, so when the FDA sort of came in and this gave me a really good transition option where we sold tailor made compounding to create true diagnostic, really, a company that's based, fundamentally on measuring epigenetic methylation or epigenetics is a platform and interpreting that data for clinical outcome.

Obviously, the way we started and the way that most people know about us is in biological age, but DNA methylation and epigenetics can go way beyond that as well.

So, tell me around, do you have any, what innovations are coming next? Are there any fourth generation clock or AI based interpretive layer, in development?

Yeah, absolutely. We've got a lot in development. So really that's what I do full time now is mainly manage our research. And for all the upcoming research and development.

And so, you know, first we did biological clocks. And I think that that is, certainly an exciting space and one that's going to keep growing. You know, actually the biggest development there is actually not a scientific development so much as a regulatory development.

There, been a couple things in the US government, particularly called Arpa, which is funding grants to get an FDA approved aging diagnostic. And so, for this, they're using, sort of a, a framework from the World Health Organization called Intrinsic Capacity, where we have intrinsic capacity domains of, you know, vitality, psychological fitness, you know, among a lot of others.

And this is probably what is going to be the basis of a lot of clocks now, because it matches the World Health Organization gives a framework for an FDA approval for aging.

And so I think that this is probably the most exciting. These are probably what the clocks are going to be trained to are these IC capacities. But really they're still judged by the same criteria, which is how predictive are they of outcomes?

How can we predict 20 year outcomes? How can we predict 30 year outcomes? How can we predict lifespan? And these methods continue to get better. And so so that is I would say from the biological aging clock side, one of the biggest developments, however, I think that, you know, DNA methylation is much more than just biological aging.

And I think that that's probably the biggest development. You know, we are now creating methylation risk scores for both diagnostic and prediction. Almost every chronic disease that you can imagine.

So that would include, you know, everything from, you know, cancer to cardiovascular disease to Alzheimer's. We now are able to predict your five and ten year risk of all of those diseases with the same blood spot.

Now that we used to do biological age, and the amount of data that we can get from this is just really incredible. That's great. And so is that different and distinct from, say, LPA Lily.

Or is it or is it that are we looking at those types of, nuance? We so yeah. So we actually have two different types of algorithms that we would call it.

One we would have is methylation risk scores. And those are just predicting disease directly. Right. So they're just going in and saying what is your risk of cardiovascular disease.

However, I think you bring up a good point, which is that cardiovascular disease might be due to a lot of etiologies. Right? It might be LP little a it might be that you have some glucose problems and insulin resistance.

And so the question is, yeah, how do we get these to be also, interpretable for clinicians to then actually affect status, on an individual basis. And for that we have a different set of algorithms that we call epigenetic biomarker proxies.

And, and actually, this is probably the thing I most excited about my entire career. We can with that same drop of blood, right? A that it comes on a blood spot card that can tell us about all of your organ systems ages.

It can tell you your immune cell subsets like flow cytometry, that can tell you your risk and diagnosed multiple different diseases. We can also predict 1700 different biomarkers metabolites, lipids, proteins, clinical values.

And we can actually when we compare them head to head, we see that 62% of the time they're actually more predictive than the surrogate they were trained on.

Methylation Risk Scores and Disease Prediction

So for instance, our LP, the delay is actually more predictive of cardiovascular disease and even measuring LPA in clinic. Same with things like systolic blood pressure.

Same with things like glucose or HBC. Is they're not all the time, but 62% of the time is crazy considering we have 1700 different variables and we can get it all from a single blood drop.

And so, so, you know, and I always joke that it sounds a little bit like Elizabeth Holmes and Theranos, but but it's actually reality now because the amount of information stored in just the molecular genome, epigenetics is pretty incredible.

We can, you know, right now it's tell you, if you're on ibuprofen or acetaminophen, we can tell you what zip code you've lived in most of your life. We can even tell you what foods you've been eating based on the metabolites in your blood.

All from a single crop. Which is crazy. And, you know, even even three years ago, we had no idea that this would be possible. But now, with the the sort of advent of AI, it's turning pretty science fiction.

That's fantastic. Wow, that is super exciting. Have you been what are the companies have been working with? Have you do you have any partnerships with companies that are doing like, Yamanaka factor studies and whatnot?

Like, like. Yeah. I yeah, tell me about that. Certainly. Yeah. The, you know, the, the epigenetic reprograming, to me is, is one of the most exciting areas in longevity.

It's actually the, you know, the big development, which made me think for the first time that longevity escape velocity is possible. Right? This idea that we're going to be able to turn back the clock longer than, you know, more than we're aging currently so that we can really extend lifespan at a pretty incredible rates.

And so we are doing a lot of that. You know, I can't necessarily mention all the companies that we're working with there, but, but the answer is absolutely.

We've even, been reprograming bone marrow stem cells with Dana-Farber, with things like valproic acid, and then

re infusing them back into the individuals to see how they're affecting phenotypes.

The, the work there is pretty incredible. We're working with most of the companies, I would say in the space that are doing that, we're even doing some skin epigenetic reprograming, work for for some of the companies with our skin clocks that we've developed now.

Wow. That's that's wild. That's super amazing. I look forward to being a part of this, in some capacity with my, burgeoning practice. Definitely want to connect with you guys, soon with regard to AI and big numbers, big data.

Are you utilizing that as it obviously has to come into play with being able to iterate quickly? You know, as opposed to, you know, bench science, which takes, you know, decades to achieve.

Now you can get there much quicker, like in silico type research. Are you doing that type of thing as well? Oh, definitely. So right now it's an internal company mandate to 20% of our time should be spent on AI.

And that goes for everyone from the the lab team to the bioinformatics team, but also our marketing and, you know, tech teams. Everyone is now incorporating this.

And so it is all over our business now. And but with that being said, the biggest use case is certainly in the modeling of these algorithms. You know, whenever we talk about epigenetics, the data set that we're really getting from the lab is basically, a million numbers between 0 and 1.

You know, each of those numbers represents the relative degree of methylation at a particular gene location. And so that number is pretty uninterpretable.

Unless you train algorithms to, to tell you what that that means. And so generally, you know, in the case of some of the early biological age clocks, it was using a machine learning algorithm to tell us, how old someone was or to be able to predict that as an outcome.

And then in the second generation clock says, became how can we predict biological phenotypes like time until death? Right. And now we're doing it for is this person have cardiovascular disease or will they develop cardiovascular disease in five years, ten years?

And so the, the generally the only way to, to take that raw data and then to get an output like that is to train a tool. Right. We're we're basically developing tools, that can inform us about how to read the data.

I sort of, you know, call it the Rosetta Stone of DNA methylation. And that's really what we're trying to do. And so the more data we have, the better.

AI, Biomarker Proxies, and Data Modeling

And obviously we have a lot of data in the million locations on every single sample. But in addition to that, we have all of the covariate data, like, does a person have a disease?

You know, even, you know, when did they start losing their hair or when did they develop, you know, x, y, z? Are they taking a certain medication. So now all of that data is being put into to these models.

And, and eventually I think you're going to have a lens of biological data, right? Just like ChatGPT is able to use language as a model, this will be the language of epigenetics, where we'll be able to input all these CPGs and then calculate all of these other outputs just from that same data set.

Wow. Wow. Very powerful. Very exciting. That's cool. Let's see let's talk a bit about, Crispr technology. Are you involved in any of if you're not doing Crispr technology, but is there any way to measure, end points specific to that type of, clinical methodology or. No. Yeah.

You know, so, so right now, you know, Crispr is, is for the first time becoming personalized, right? I think maybe even the a few weeks ago in the news, we, we saw that, you know, there's an individual Crispr therapy to solve, you know, newborn deficiencies, which is awesome.

But already the, you know, we're not doing a lot in the genomic world for rare disease. But in the epigenome world, there are now multiple companies who have been funded with hundreds of millions of dollars to then go in and genetically reprogram.

So, so just like Crispr, be using another Cas9 system to then change methylation at a particular location. So, for instance, I'll give you an example.

You could go into, for instance, cancer genes and then say, you know, we want to turn on this tumor suppressor gene to increase surveillance of cancer and prevent prevalence.

And so, so that is, so the race into the gene editing of epigenetics is also fully underway. And there are some really cool things. Anecdotally, I always like to mention one of my favorite things is that this whole idea of evolution, right, where we have survival of the fittest, is sort of being, changed a little bit with this idea of epigenetics because we can see signatures of, for instance, the Rwandan genocide or the Holocaust or the Irish potato famine in our epigenetics.

And these sections of the epigenome behave very differently than regular epigenetics. They behave more like genomics and the fact that they're passed down.

You know, this is why we have things like, you know, ducks imprint, right when they're first born. These are epigenetic mechanisms. One of my favorite stories is even, mice who got exposed to the smell of cherries, you know, every.

And they were shocked every time that they were exposed to smell cherries. Even five generations later, when those mice smelled cherries, they would still shake and have fear behaviors.

And so, so, so with that being said, epigenetics can also be a little bit like genomics and the fact that it can be passed down and inherited, in those regions, you know, have been postulated, we call it the imprint.

And it might be the reason we develop things like Alzheimer's or autism or birth defects, and some of these other things which could then be, again, genetically edited, to, to fix some of those behaviors.

So, so we're not directly working on it, but ideally we'll, we'll be able to do is define the exact regions we need to edit, and then be able to work with a company that does that to then take it to clinical trials.

Wow. Excellent, excellent. Wow. Super exciting times. Okay, let's go a bit more, esoteric, more philosophical. So what are your thoughts on the whole process?

The potential of, longevity escape velocity? Let's, let's give a bit of a primer on what that means for our audience and then lean into, what are your thoughts on that?

What do you see? Knowing what you know, you've done probably one of the deepest dives on this subject matter than anyone. Do you see a ten year timeline?

A five year timeline? What does that look like for you in your mind? Yeah. You know, even six months ago, I would have given you a very different answer.

Just to give you an idea of how quickly it's moving. You know, I have been, for a long time, I think, a longevity skeptic. And again, I know that that's probably surprising, given my company.

But, you know, I think that, the reason we just try to try to search for biological age tools is because it's so hard to

quantify and define, but yet it's so important for every disease.

It's still the, you know, the number one risk factor for almost every chronic disease and death. So, so we've been trying to find these tools.

Epigenetic Reprogramming and CRISPR

And there are things that make me a skeptic. Like for instance, caloric restriction and rapamycin are still the biggest effect sizes in mouse models for aging.

And so, you know, we, we these have been around for a long time, and we've still yet to improve on those, you know, in a major way. And so I get skeptical there.

But then I see some of the things that are happening in the epigenetic reprograming field, and that has has drastically changed my, my outlook on this.

You know, I think, Davidson Claire's been doing work to restore vision, you know, in certain types of blindness, conditions, you know, particularly some of the same blindness conditions that are caused by GLP ones, actually, which is, you know, maybe more on the rise and more prevalent.

But but some of the things they've been doing there to restore function, via epigenetic editing is to me pretty incredible and shows exactly the type of impact we could have for people who have now been blind but have vision restored.

That is an incredible breakthrough. And I think just, an example of what some of the Reprograming can do. And so, I would have told you it would, be a long time before any of us are, on average, living to 120 or above.

And, you know, now, I think that it will certainly be the reality of my children. I think that that is certainly possible. It's really interesting to see how they're giving those therapies to their their patients, their mice and their non-human primate patients through AAV vectors.

You know, adenovirus. But the idea of potentially making it a pill that you could take, you know, that the masses could take something as simple as a nutraceutical of some sort that would affect that same change or, you know, across multiple organ systems is really fascinating to me.

It seems like, you know, going beyond Mars, you know, it seems that that that's really far fetched. But you got guys like Davis and Claire talking about it at large conferences, and it's it's quite mind blowing.

I'm having a hard time believing it. You know, I really want to believe it, because I've seen disease processes at the at their endpoints. And that's all I know in clinical medicine for heavy practice as a physician assistant for 20 years and going to medical school late in life, I think that, you know, it's possible, but, man, it seems like it seems like, you know, I'm the Wright brothers looking at a rocket flying across the universe, and I have no idea what that thing is or how it works.

Exactly. Yeah. I, there's a paper here we just published yesterday. From Ship Bioscience is a company in the UK. They made one genomic edit that was the equivalent of a lot of these reprograming cocktails with better efficacy.

No, no, sort of risk profiles for cancer development. It's one genomic edit for massive implications. And so they're, they're now taking this to the I mean I agree it, it is looking at a very strange technology.

And the implications I think are are just going to be combined with AI, for, for massive, massive changes. So with all the interventions that are available now in terms of measurements and whatnot, how do you see therapeutic modalities, moving in the right direction with regard to this treatment?

Yeah. So, so first and foremost, I think with therapeutics, this is what we've been trying to do is to get a universal

measuring stick, right, with these biological aged clocks.

That is really the main purpose. And so now we've done some work with Yale in particular, Albert Higgins Chen's lab. We've created this platform called translate.

So we've now powered that, we published on it with 51 different aging interventions, everything from hyperbaric to stem cells. You know, to, rapamycin.

And now we've got over 120 different interventions in that data set. And so the good news is that now we can sort of compare everything head to head across the multiple different age measurements.

And so do not bury the lead too much.

Longevity Escape Velocity and Therapeutic Interventions

I think people want to know, you know, what has actually working. And I hate to tell people that a lot of what we've found right now are the things you already know, right?

And again, that's not necessarily a bad thing, but, you know, in terms of, you know, proper diet, exercise, proper sleep, you know, those things are pretty intuitive, but it's good that we're seeing them work in the clocks because it gives us a basis of comparison to know, hey, we're measuring the right thing.

Right. But, you know, in the more exotic things, you know, we found some really cool effect sizes from things like with hyperbaric oxygen. That's one of probably the biggest movers of some things that we've seen right now.

You know, we are rapamycin data sets I'm very hopeful for, but they've been underpowered. A little bit. And so I wouldn't speculate too much on those.

But then, I would say there's also a couple other really interesting things, like, you know, vitamin D almost always works in everyone. Omega threes almost always work in everyone.

Those are again pretty intuitive. But then we have some other more exotic things like even, you know, taurine or Alfred to glutamate, or you know, even some analytics like set a different course.

Adam had some pretty good effects. But even not in the first three months, it takes even longer to see some of those. So, it's we're learning a lot, but I think the great news is now we can put all these interventions all together, we can harmonize them together and then use these universal measuring sticks to actually give us good behavior.

And then with these algorithms ongoing now is to also then be specific enough to make personalized recommendations so we can predict treatment response.

It's it's a little bit like a pharmacokinetic test. But think of it for everything that you do in your life. Okay. Tell me how I might go about, engaging your, your skill set and your team within the context of my practice or for any other physician or clinician out there that would want to engage with you.

Yeah. So, so ever since we built this, this network of, you know, health care providers with the pharmacy, this has been our major network. So this is who were we're made for.

We think a lot of these things are so complicated in practical use. They certainly should be guided by someone with medical expertise. And so, we if anyone would like to, to start on our platform, we do lots of education and clinical training to talk about all the developments that are happening across, you know, every single month of change.

And so you can go to, to diagnostic.com to get started, but we love to guide and help physicians implement our testing. That's great. Do you see yourself putting together like a formal, certificate program or some sort of like, you know, formal training as opposed to end under the website?

I mean, I'm excited. I'm all in on that, but it would be great to kind of go super deep with that training. Do you have, people on the team that are teaching that kind of thing?

Oh, absolutely. And in fact, you know, we think that the Epigenomic movement is so much bigger than even just us. We've tried to get help, I would say give our assets and resources to nonprofits as well.

So there's in particular the, Clinical Epigenetic Society, that we, are helping with, to try and get started to help educate physicians across not just our testing, but even some of the liquid biopsy testing that is now becoming much more prevalent to, to use, you know, other tests that might be specific for Alzheimer's.

You know, the epigenetic revolution is sort of here from multiple sources. And I think that that we need to, to help educate as much as possible. I know when I was in medical school, we didn't have a single day about epigenetics.

You know, probably only 30 minutes in my undergrad. So this is just that new. Wow. Excellent, excellent. Well, I look forward. Sign me up. I'm ready to go.

Thanks so much for joining us. How can people reach you? Aside from you got through diagnostics, any other place, within social media that you might be found?

Yeah, certainly. I have a Twitter, which is, I think Ryan Smith. If you'd like to find me, but also two diagnostics is probably one of the best points of contact.

You also find me on LinkedIn. Excellent. Great. Do you have a podcast or anything like that?

Clinical Use, Training, and Closing Remarks

I don't, I, but but maybe in the future, maybe I'll get a nice set up. I do have. Awesome. I look forward to seeing that and seeing. Yeah, I've watched a number of your videos and interviews in the past, so this is really interesting. It's a full circle for me to be here in the room with you having this interview.

Such an honor, such a pleasure. Thank you for joining me. And, hope to talk with you soon. Yeah. Thanks so much. Appreciate original. All right. Take care. Bye bye.

Thank you for watching and or listening to the Every young podcast. This podcast is for educational purposes only and is not intended to diagnose, treat, or cure any disease.

I'm Richard Hanley, a licensed and board certified physician associate pack, trained at Harvard Medical School and the USC Keck School of Medicine. Well, I do hold two doctoral degrees, including the Doctor of Medicine and Doctor Phil Science.

I'm not a licensed physician. I also hold a master's degree in health care quality and safety from the Harvard Medical School. I bring over 30 years of clinical and executive leadership experience.

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That said, the views expressed herein are entirely my own and do not represent the official views of Harvard Medical School. Always consult your own health care provider for making any medical decisions.

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