CUTTING EDGE Health

Welcome to the *Cutting Edge Health Podcast* with Jane Rogers, where we discuss science to help prevent cognitive decline.

Jane Rogers: Hey, everyone, thanks for making the time to tune in for this episode, whether you're listening to the audio podcast or watching the video version on YouTube. I learned so much in today's show. We all know how many birthday candles should be on our cake, but do you know your biological age? That's how fast your cells are aging. You ideally want your biological age to be seven years younger than your chronological age because studies show if you're aging that well, you cut your risk of developing an age related disease in half.

Our guest today is Ryan Smith from True Diagnostic, which offers biological aging tests for folks like us. Ryan, I would like to welcome you to the podcast. How are you doing today?

Ryan Smith: I'm doing well. Thanks, Jane for having me.

Jane: Good. Tell me about your company, True Diagnostics. You've only been around since 2020 and you're doing really exciting work.

Ryan Smith: Yes, well thank you for that. The company is very new. It was in 2020, really based on one idea, which is that we wanted to provide some of these really exciting age-related algorithms to our network of clinical physicians. Due to some move of previous businesses that we've had before, we've always been very involved in the process of educating physicians in this cash pay integrative health market, a lot of whom would consider themselves probably anti-aging physicians with some of the advent of this technology over the course of the past decade.

It really started in 2013. We really saw the first application in September of 2019, where they published the first-ever clinical trial showing reversal of these age-related diagnostics. We thought this is by far in the literature, the most exciting way to quantify that aging process. We definitely have always had this idea that age itself is a disease and one that if can be appropriately measured, can then be appropriately managed. We really wanted to provide some of the new science and the ability to measure these aging rates very, very specifically to that clinical community.

We started that in July of 2020. We started the company in March of 2020. We built a lab that's CLIA certified in all 50 states. That's the state-of-the-art genetic and biomolecular infrastructure to do a lot of this testing. In addition to offering that to clinical providers, during the rest of that year, one of the other questions we've been really focusing on is how do we learn more about what insights are able to reverse that

epigenetic aging process. With that, we've created a lot of clinical trials and really trying to answer that question now, which can be a little bit frustrating, because now we do have really accurate and really amazing methods to determine age, but we still have little to no idea about the best ways to reverse it. That's really what we're focusing on at this point.

Jane: My community cares about preventing cognitive decline.

Ryan Smith: Absolutely.

Jane: Why should they care about, of course, how many candles are on your birthday cake? What's your chronological age? You usually see people who are older getting cognitive decline, but what you are saying is that it's your biological age or epigenetic age, that's going to be the driver for disease, age-related disease, like Alzheimer's and dementia?

Ryan Smith: Yes, absolutely. First and foremost, the age is the biggest risk factor for all chronic disease, including any type of neurocognitive-related issue. As we probably all know, we probably know people in their 70s, who look like they're in their 50's-

Jane: Exactly.

Ryan Smith: -and vice versa, right? Chronological age is not the best method to do a lot of these diagnoses. Really, a better method is this idea of biological age and the age of the body. This has been something that people have tried to develop for a long, long time, even in the 1920s. I will use this as an example. They were doing biological age by saying, "Your chronological age plus one year for every pack per day you smoked." There have been some very, very crude methods for that for a long time.

Now, essentially, what is happening is that these are becoming very, very precise due to this new idea, new biomarker, that there really is just now happening, this idea of epigenetics, which really is where genetics was over 30 years ago.

Jane: Let's unpack this. There's a lot of information and it's new science and I think It's unfamiliar to a lot of us. We should get a test done that measures our epigenetic age. My audience is really interested in how to stop aging because then you, hopefully, stop the diseases of aging, like cognitive decline, memory issues, Alzheimer's, dementia, all of those things. Why is it important that I know my epigenetic age and how do I find it out?

Ryan Smith: It's important because age is the number one risk factor for all those things you mentioned. Biological age is an even better risk factor, particularly if we

look at if you're an advanced or slowing de-accelerated aging process. The idea would be that these epigenetic markers we're talking about are not like your genetic markers, like APOE3/4 et cetera, these things are changeable. Through diet lifestyle intervention, we can then look at what is affecting risk of not only aging, but also disease, to then see how we can mitigate that via lifestyle, diet interventions, pharmaceutical therapies, really anything in our lives, which might mitigate that.

We go through that process by really measuring the DNA. We're not measuring the actual sequence, what we're measuring is the expression of how those genes are turned on and turned off. The majority of that, the way I was to explain is every cell in your body has the exact same DNA. If we were to take a sample of your skin and your hair, we get the exact same DNA sequence. However, all the cells in your body have different epigenetic expressions because they all want to behave differently. Your skin might turn on genes to make collagen, whereas your heart cells might do it to make actin or some other muscle filaments.

All these different cells are different and by analyzing these patterns this new biomarker of methylation, which is thought to inactivate gene transcription. Generally, if a gene is methylated, it's turned off. The ability to look at methylation is only a relatively new thing, especially at scale, we have over 29 million different spots in each cell where something could be methylated. They can all be methylated at different percentages. What we really have now is a way to really build a really large-scale data set, but the problem is the interpretation of that data set. How do you learn what those markers mean and how do you apply it to an outcome?

Aging has been the main source of a lot of this research for a long time, mainly because it has such a high correlation to those methylation marks on your DNA. As a result, this has been used as a surrogate method for a lot of things, and really has changed this philosophy, where this idea of epigenetic methylation and managing that can manage risk factor for every chronic disease, and especially a lot of those neurocognitive ones as well.

Jane: It's easy to get tested, right? You just you put a little bit of blood in a vial, and you

Ryan Smith: It's that simple.

Jane: It's that easy.

Ryan Smith: Not quite as easy as a typical DNA where you're doing saliva or the buccal cell. Just a few drops is all we need. The reason we use blood is because that's how all of these interpretations have been trained. We need to use blood to make sure that we're giving you the correct age. If we were to use, for instance, a

breast tissue, we get much, much higher age than your blood. If we were to measure your brain tissue, you get much, much lower ages than blood. The tissue type matters and blood is definitely what we recommend, and will probably continue to be a blood test for several years.

Jane: You send it off, you wait a little bit, you get this result that says, "Haha, I may be 60, but I really am 70 in my aging," or whatever.

Ryan Smith: Yes.

Jane: That's kind of scary. Yes, it is. How can you change that? Let's say you get a report back and you are aging much more quickly than you thought you were and you want to impact it.

Ryan Smith: Yes. As I mentioned earlier, that's still a little bit of a question mark. There are some things that we absolutely know, though. One of the things I should mention is that really the goal that we're trying to shoot for is for everyone in the world to be seven years younger biologically than they are chronologically. If you're 50, we want you to be right around 43. The reason being is that if everyone in the world were seven years younger, biologically and chronologically, we've cut disease in half 50% of people would no longer be sick and so you can--

Jane: You're kidding.

Ryan Smith: No, the population level impacts of aging are incredible. In addition to that, if we just slowed the aging rate by 20%, we'd save the US over $3 trillion in healthcare spending. This idea of age as a disease is one that's not been, I would say, accepted as an ICDTIM code, but it's starting to be accepted as its own independent disease process. That is really exciting because the impact we can have is great. Whenever we're talking about those things, that's really the goal we're trying to shoot for. How do we get you to be seven years younger biologically than chronologically?

Jane: Are you seeing that with some of your clients? Are you seeing in the follow-up studies that they are able to decrease that biological age?

Ryan Smith: Definitely. Right now, there are only around six or seven interventional studies that look at a baseline, a treatment ended an outcome. They're that many, but we've got 30 ongoing, so quite a few. A lot will come out in the future, but one of the things we know the most about, is by looking at data sets from the past where they might have stored their blood samples and biobanks for 50 years, and then they've developed a lot of these outcomes. What we're able to do with that is look at a lot of the traits and behaviors which are associated with better or worse

aging outcomes. We know a lot epidemiologically, to say, “Hey, we know that some alcohol is good, but too much is definitely bad.” We know the same for exercise.

A lot of the things we found out on this epigenetic level from large-scale populations are relatively intuitive. We know things like stress management is great, getting more than seven hours of sleep per night, eating mostly plant-based diets with anti-inflammatory related diets, and making sure your immune system is healthy. All of these different things are relatively intuitive things we know. There are also some very, very exciting things that we're finding out as well, in particular, on how to reverse some of these markers. One that definitely strikes me as one of the most exciting particularly for your listeners, is something called plasma apheresis or plasma exchange.

The reason that, I would say, it's probably relevant to your viewers is the same therapy has been studied at very large scale for reducing Alzheimer's risk. The studies, just to let you know, started in a very strange way. They started by connecting the vascular systems of old mice with young mice. They sewed their blood systems together, and whenever they did that, they found that the old mouse actually became younger. Had thicker hair, had better mental processing speeds, all of the markers of age that they have seen in this old mouse, were rejuvenated, and vice versa, some of the markers in that young mouse actually became worse. It actually showed advanced and accelerated aging. This idea was that, hey, there might be something in the blood, which is causing these aging rates and so one of--

Jane: How do you-- I'm sorry. I have so many questions. Go ahead. I didn't mean to interrupt. [chuckles]

Ryan Smith: Well, that is a hard experiment to do. It requires surgery and so what they started to do is to change those protocols in some form of fashion. One of the things that they started to do was to do plasma apheresis, where they take out the plasma. In very simplistic terms, they filter it and then reinfuse it with a couple of other products like albumin or serum IgG. When they do that, they found that you can really limit a lot of those aging rates in acceleration.

One of its first applications was with multi 24 hospital trial study. We're looking at Alzheimer's, and it's called the Grifols study. What they found was that it didn't have, I would say, a reversal of Alzheimer's, but it could help prevent it, and that was really, really exciting. That therapy in particular, for us, when we've measured it, has had multi-year age reversals with just even one or two procedures.

Jane: Oh, my.

Ryan: Yes, so whenever we think about that seven-year age gap as a benchmark, having something that would reverse it multiple years is something that's very exciting.

Jane: Tell me more about that. Does someone just get that at an alternative clinic or do you-- How does that happen?

Ryan Smith: Unfortunately, at the moment, it's not very commercially available. I think that with the growing amounts of data about how positive that therapy is, not just for aging or not just for Alzheimer's, but for a variety of other conditions like autoimmune, it will become a little bit more prevalent. At the moment, there are a few people doing it throughout the world, but it's also very expensive because it's not commercialized on a large scale. A lot of the things that we're doing are very, very innovative and trying to get some of those data sets, but that is one that excites us quite a bit. There are a lot of other therapies as well.

Jane: Let's go back to how you determine epigenetic age. We've all heard about telomeres. How does all this fit into your algorithm for determining a biological age?

Ryan Smith: Yes, absolutely. The first algorithms that started, started really, the publication, in 2013, and this was done by Dr. Steve Horvath at UCLA. What he did to create this age algorithm through epigenetics is, he basically took a lot of different patients, got methylation data on them, and then basically put all those methylation spots that he was looking at, into a computer learning system so he was using artificial intelligence. It basically said, “Hey, create a predictive algorithm, which is able to get as close to predicting that chronological age as we can." That came out in 2013 and I think he'll probably win a Nobel Prize for it. I think it's that exciting.

One of the interesting things was, it was predicting chronologic age and so whenever this first came out in 2013, it was immediately used for things that were not medical or clinical on origin. They were used for things like dating DNA at a crime scene to see how old someone was at a crime scene, or testing refugees to see if they were adults or minors, and then therefore eligible for asylum, particularly, in Europe with a lot of those Syrian refugees.

It was already applied commercially to some degree, but one of the biggest problems with that is it was trained to predict chronologic age. If we wanted to predict-- We have already talked about some of the issues with chronological age as a biomarker. Really in these second and third generations, they changed what it was trying to predict. Instead of trying to predict chronological age, they tried to predict health phenotypes. Are you likely to develop disease or are you likely to die?

With those, they look at all these different marks from the DNA and they pick out just a select few that are most correlated to that outcome. Whenever these markers change, it usually means that you're aging or you're proceeding closer to that outcome. We have a standard across lifespan and then we have where you should be. The idea is that that by training it against those algorithms, you can predict disease and death, which is as a result of these aging markers.

At first, it was thought that these aging markers might, I would say, be correlated to those outcomes. Now it's almost thought that they're causative. They're actually the things that are going and causing some dysfunction, which might lead to premature aging in the first place. We're measuring a lot of different DNA locations. We're measuring over 900,000, and in each of those, really that raw data output that we're getting is a percentage of methylation, so really a number between zero and one. With that, we use these mathematical algorithms to then predict those outcomes of biologic age.

Jane: Tell me a little bit more about this. You've watched people change their biologic age. If you've measured it, you can change it.

Ryan Smith: Yes.

Jane: You've watched them change it.

Ryan Smith: Yes.

Jane: Tell me about your day. You hear from these people. What do they tell you? How does it change their life?

Ryan Smith: Yes. One of the things I always like to say is that a lot of what we do is based on relative risk. We talk a lot about percentages. The idea being is that the younger you get, the more you're reducing your risk objectively, of all of these other outcomes. Everything from Parkinson's, Alzheimer's, to cardiovascular disease, to stroke, to cancer, all of these things are reduced if you reduce your age. The idea is that, hopefully, no one should ever be satisfied. We want them to compete with themselves to get that as low as possible for as long as possible. A lot of our clients who are using this now are using it as ways to say, “Hey, are these anti-aging interventions I'm doing, all this work I'm doing actually working? If so, what is maybe working more than others so I can prioritize and decide what type of treatments I actually want to do.”

There's no better way to do this than personalized medicine, where we actually will take a baseline, then someone might implement some type of protocol or procedure, say it's fasting. They might try to implement that for three to six months and then retest, and to

see what type of trajectory they have for some of those samples. Those are always in a trial, which are always a little bit limited in how you can apply them to the general population.

We're starting to see some trends which then will help us influence to make recommendations on how people change those lifestyles. We already know things like the Mediterranean diets are great at causing lower aging rates, we know that fasting of any type or just core restriction, so not just eating less food is a great way to reverse your biological aging process, although it's something that not everyone wants to do. Those are, obviously, great things that we know right now and some things are becoming very clearly definitive. Others are looking like they might have some individual components.

This is as I mentioned, definitely in its infancy but as we grow, as this biomarker grows, it'll go way beyond aging. Even right now we can do some really interesting things beyond aging. For instance, we can predict schizophrenia or tell if you have ADHD. We can tell you even when you're going to die actually with an algorithm called GrimAge. I think the idea is that even outside of aging, this biomarker is a very, very new one which will yield and change really every area of medicine.

There'll be predictors for neurodegenerative disease, there'll be predictors for how you might score an athletic performance, even things maybe for IQ and mental processing speeds. We'll be able to predict a lot of that with just one drop of your blood.

Jane: I can see your office environment now, do you have some pool going on? "Well, Ryan, decreased his biological age by 10 years," and you're the winner so far. [chuckles]

Ryan Smith: Oh, absolutely. Unfortunately, I'm losing that battle. I'm actually aging myself so I'm still trying to turn back that clock. Absolutely, we definitely have records in each of these things. One of our favorite algorithms to look at is not one that tells you your overall age, but one that tells you at this moment how fast you're aging on a sort of a biological year per year basis–speedometer in aging.

The reason we really like that one is it's very, very predictive of disease outcomes. For instance, even if you're aging slightly above one biological year per year, you would increase your risk of death over the next 7 years by 56%. You increase your risk of chronic disease diagnosis by 54% over the next 7 years. Those are some big increases in relative risk, all the results of this aging rate. Also, one of the other things we like about that is it it's a picture of the current versus the entire picture which allows people who maybe have not lived the best lifestyle, or it might have already accelerated biological aging, it gives them a target to say, "This is what I'm doing now." Not the

overall picture but controlling what I can control, how can I decelerate my aging to the best degree possible.

That is an algorithm we really, really like. We developed, I should say, licensed that from Duke and Columbia.

Jane: What are you telling your relatives right now? What do you tell your mom and your dad? You have the information, your company has information, science has the latest that can really change the trajectory of their lives. What do you talk about at the dinner table?

Ryan Smith: Absolutely. My parents were one of the first people we did They're in their late 60s and so trying to protect them. Again, I've made APOE3/4 variant myself. They've had their parents with dementia and Alzheimer's. I think that your story is very close to my heart as well and for them and so with that being said, I think that we talk about a lot of different things and a lot of different categories.

The way we usually talk about that is as we talk about the hallmarks of aging. Generally, there are around nine hallmarks of aging and, unfortunately, we think that it's best to address all of them at the exact same time and so try to talk about a lot of different things. For instance, telomere as we talked about, telomere attrition is one of those hallmarks of aging. As we're getting older, our telomeres get shorter. As those telomeres get shorter, they then go into things like senescence which is another hallmark of aging.

We try to treat a little bit of everything and try to find out the best protocols for each of those hallmarks of aging. We do have some recommendations for things like senolytic treatments to reduce the burden of those senescence cells which cause that inflammaging process. We recommend things to help reverse proteomic dysfunction or to help with nutrient-sensing. A lot of these hallmarks of aging are what we take from an approach.

If there are things I would recommend for everyone, the one definitive thing that I think everyone can benefit from is caloric restriction. We know that caloric restriction is a great way. I know it's a very hard thing to do but with that being said, the benefits are overwhelmingly positive. It's something that doesn't cost any money, actually probably saves you money, and will then help with your overall aging, in lifespan and healthspan.

Definitely, I would say aging. I do recommend some pharmaceuticals and supplements for my parents as well. Things like DHEA seem to have a major impact on this. We hypothesize that might be due to its effect on mitigating cortisol and some of those stress-related hormones. We recommend things like that. For people who have MTHFR

genetic variants,we might recommend things like flavonols, citrus bergamot or green tea extract to give those cofactors to help remove methylation, to give your body the necessary fuel it needs to do its reactions and jobs.

There's a lot of different recommendations, a lot of which we think can work for everyone. Unfortunately, at the moment, we're not to the point where we can make specific recommendations to say, "These markers on your genome are causing you to age. We need to reverse those markers with this therapy." We can't really say that right now. What we can say though is, for instance, that we have different algorithms for aging, so different ways to break down this idea of aging and then different recommendations on how to treat each of those individually.

Usually, what we do in these analyses is we first say, what is the worst category for you? What are you performing worse then and then how can we make efforts in those areas based on the scientifically published data that we know will reverse those metrics?

Jane: Things like NMN, things like thymosin alpha, things-- I read about these things. I read David Sinclair's book on longevity, fascinating research of what he's doing. Those are some of the things that are on the horizon for all of us?

Ryan Smith: Definitely. Then I can tell you in our independent data sets we do see a mild positive benefit with anything like NMN or Nicotinamide riboside or NAD. Anything that increases NAD we do see a slight benefit from in some of our early data sets. Those things are exciting and I think that Dr. Sinclair's hypothesis about the importance of sirtuins is a really, really exciting one. We're activating those same sirtuins via things like resveratrol or some of those other things.

We don't really know yet I think but we're definitely hoping to have the data behind that. Then even things like thymosin alpha 1 which we know have great immune-related benefits can really help that as well. Honestly, it's one of the biggest confounders of our testing too is that it does depend on your immune system and your immune cell subsets. We do have to control for that but with that being said, those two things are definitely things that people are using currently with our testing to try and reverse their epigenetic age.

Jane: I thought it was fascinating. The pictures that you have on the website of the people who were born in 1972 and how quickly they are aging. There are some of them that are aging so quickly, others are pretty average and others just look really young. We all see people like that. Can you tell us about those images and how you came about them?

Ryan Smith: Yes, definitely is one of my favorite things to talk about because as I mentioned, we talk a lot about relative risk and that can be a little bit hard to understand. If We tell you that you might be at a 14% increased risk, what does that really mean to you? This is different because it actually shows you the impact of aging on things like facial images. This cohort that you referenced started in New Zealand in 1975 whenever over 1,000 patients were three years of age. These children were really starting to be inducted into this cohort with the purpose of measuring their aging rates throughout a lifespan.

Some of these algorithms have been developed by looking at multiple different individuals at one point in their lifespan. This took a different approach which is trying to say, "Hey, let's look at all of these individuals across their lifespan and see how their markers are changing on an individual basis." That was really, really exciting. Something that's never been done before. Now here in 2020, these individuals are 45 years of age or older. We've followed up with these individuals and one of the things that we've done to investigate how their aging is we've taken composite facial imaging of all these individuals.

What we can see whenever we do this diagnostic is that the rate of aging I mentioned–people who are aging at a slower rate have significantly younger facial appearances. Whereas the people who are aging at a fast rate have significantly older facial appearances. They look almost 25 years apart. In fact, because they probably are, at least biologically, because some of them are aging at a two year per year basis, while others are aging at a point six per year basis.

Over time, that definitely accounts for a big change. It's not just with facial aging, but it applies to every type of organ system as well. We saw the same things for things like muscle mass and sarcopenia. We actually saw almost, on average, five points of IQ loss in patients who are aging at a rate of two years per year. All that to say that you're aging affects every other process of your body, including how you look. Another reason that we really like to say you want to manage this process as early as possible.

Jane: You mentioned you're doing this because you've got the APOE4 gene heterozygous, homozygous.

Ryan Smith: Yes.

Jane: Yes, and so this was a personal ambition for you, isn't it?

Ryan Smith: Definitely. I've always had a special place in my heart for neurodegeneration, but I think that the rate of aging metric that we talked about, that one is incredibly good at actually predicting the onset of neurocognitive

dysfunction, whether it's mild cognitive impairment, or it's actually an Alzheimer's diagnosis is extremely highly correlated. That one is, again, one of our favorites, because it can show us how we're progressing to that metric.

For me, one of the, and even for my parents, what we're really trying to do is to address as a primary concern that rate of aging, how do we get that rate of age as low as possible. Even above things like the overall biological age because it's probably a little bit more accurate at picking up some of those factors of neurocognitive dysfunction. One of the other things that we're really doing even outside of aging is we're looking at something called the imprintome. These are basically areas of our DNA which are inherited from a single parent, but they're not DNA sequences that we inherit, they're actually DNA profiles, methylation profiles, so they might be turned on and turned off.

It's thought this imprintome might be one of the reasons that we see, essentially, advanced Alzheimer's in certain populations like Latinos and African-Americans, especially compared to Whites because what happens is even in early childhood development, even when we're in the womb, we're exposed to some of these stress markers, which then might change the expression of these genes. Those expressions of those genes are highly correlated to outcomes like Alzheimer's or even autism, a lot of these brain-related genes.

We're not just looking at aging as a way to mitigate risk of Alzheimer's. We're also looking at other methylation marks, particularly even in early childhood, which might influence that as well, and then give us a much more cohesive picture of all the reasons we would develop cognitive dysfunction.

Jane: The takeaways from this for our audience, how often should you get your biological age tested?

Ryan Smith: I would recommend it no more than twice per year. In order to be sensitive and actionable, you do need larger periods of time to make sure that it's accurate. I would say no more than twice per year, the majority of people who do our testing will do it once per year, unless they're trying to do personalized medicine to see what works for them, and then they might do it for intervals. Generally, the idea is you can't manage what you can't measure, right? If you don't know where you're at. You don't know what's working for you and what's not, and we know that there's so much variability from person to person that some things might work for someone and others might not.

I think the idea would be, get a baseline, then the take-home message is that if aging is your number one risk for all chronic disease and death, if you want to do one thing to reduce your risk of all of those risk factors, try and reverse your aging rate. In order to do that, you need to know where you're at, and then try his best to implement the quality

lifestyles that we already know, to then reverse that process and then measure on a yearly basis to make sure that you're staying up to date and you're reversing that aging rate.

Jane: Ryan, thank you for your time. I've learned so much. It's really important work you're doing.

Ryan Smith: Yes, thank you so much for having me. I know that a lot of these things can be a little bit esoteric and complicated as we talk about mechanisms. If there's one takeaway it is that definitely consider aging itself as a primary outcome to manage. I think that is the one thing we would encourage everyone to do because it can impact their aging rate and by doing so, it can have massive positive health benefits.

Jane: How old are you going to live? [laughter]

Ryan Smith: Again, as I mentioned, I'm accelerated-aging so I'm probably not the best one to ask but, but hopefully, with some changes and with some effort and with more knowledge about what changes these things, we'll do at least 120. [chuckles]

Jane: At least 120. I'll be there with you.

Ryan Smith: [chuckles] Perfect.

Jane: Hey, Ryan, thank you for your time. I really appreciate it so much.

Ryan Smith: My pleasure. It's great to talk to you.

Jane: You too.