Introduction to Longevity and Telomeres

Welcome, everybody, to this edition of the Exponential Longevity Summit. I'm your host, Doctor Jeffrey Gladden. And here we are, as always discovered, discussing.

Here we are, as always, discussing leveraging AI to outlive disease and oblivion for a lifetime. And today I'm joined by, a gentleman to have a lot of respect for Doctor Joseph Rafael.

He's been in the longevity space for many years. And when I first started getting into the longevity space back in 2012, he was already there. And, has been instrumental, I think, in bringing a lot of things forward with regards to the importance of telomeres and the immune system and immuno senescence.

So Joseph was great to welcome you to the show. Thank you, Doctor Glenn, it's great to, to have, to be on your show and, talk about stuff that's near and dear to my heart. Yes.

I have been in the field a long time. We won't tell anybody how long. Yeah, okay. Well, actually, that's a bragging right. So, Yeah. How long have you been in the field?

Started practicing longevity medicine, which was back then called anti-aging medicine in 1998. Okay, okay. Good for you. So that's, 26 years. So good for you.

So tell us. So tell us a little bit. You know, when I got into, went through my own health crisis in the 2000s and then, you know, transitioned out of interventional cardiology into, what's become gladden longevity.

One of the first things that I was reading about was really the impact of telomeres on longevity and health. And then, you know, there were some papers that came out that talked about, well, maybe telomere length isn't all that important because, you know, it's not as reliable of an indicator for chronological or biological clock as maybe DNA methylation.

Are Telomeres Still a Useful Biomarker?

And I always looked at that with a little bit of a jaundiced eye because I think short telomeres are always a problem when they show up. So I was just curious, what's your what's your take on the telomere story today?

Yeah. Well, I think you characterized it very well. You know, when when they first came out, it was, the new kid on the block, you know, when it became commercially available and people were talking about how you it was your molecular clock, your ticking clock.

Every time the cells divide, feelers get shorter and it's short enough, the cell stop dividing. And then, a lot of the aging process starts to accelerate.

If you take telomeres as a way to predict chronological age, they are nowhere near as good as the first generation epigenetic clocks. The Horvath clock, the original one.

That's because those clocks were trained on chronological age that you don't really want something that's perfect. Predicting chronological age because, well, we already have problems with age.

Exact. Yeah. And I just wonder about about biomarkers for you, for your audience if you haven't talked about that much, you know, our biomarker has a score of zero rebellion of zero doesn't correlate with age at all.

The parameter you're looking at, one that has one of one, is 100% correlation with it. That's close to the genetic

clocks, which can be as high as 0.98.97.

What you want is one that has a correlation in that maybe 0.5, 2.8 range, where there is difference on both sides, because that captures the biological difference in aging between individuals.

So you really don't want a perfect clock. And you know, telomeres are somewhere around 0.5 or so. But, you know, now the epigenetic clocks are all moving away from the original first generation of our bath clock.

And instead of training them on chronological age, they're training them on things like immune cell subsets. They're training on telomere length. They're training them on blood pressure.

Like Morgan Levine's clock, which is called, you know, age is trained on nine routine. Chemistry and CBC and CRP markers that predict logical age pretty well but also predicts mortality.

And so but the, you know, the prediction bar squared, it's come down quite significantly when you do that. But then they become much more biologically, useful.

And I agree with you about telomeres. I mean, when Carol Greider once said she was one of the Co laureates for, the Nobel Prize in 2009, along with Lisa Blackburn, that, you know, telomere lengths don't mean anything because clinically, because, you know, you can be 40 and have a killer length of a 70 year old or 70 and have a killer like so for you, I would ask Doctor Greider if you had to choose which to your life would you rather have that of a seven year old or a four year? Right.

I dare say she would say that of a 40 year old. It's an interesting point. It's an interesting point because. And the audience should understand that, telomeres, which are these end caps on the chromosomes that are every time a cell divides, basically some of those base pairs are clipped off.

And the idea is that when those when the telomeres get short enough, then it sort of signals the cell to become senescent or to be old or to stop dividing.

And then from there it can go into being an inflammatory cells, secretory associated or a senescence associated secretory phenotype, which basically is putting out all these cytokines that basically accelerates aging.

Right. So we we know that the telomere shortening has an impact. It's also interesting when telomeres shorten, they have another impact on another hallmark of aging, which is a you know, your mitochondrial function gets shut down.

So we know that we know that telomeres and your immune system gets in a good senescent. Right. So. Excuse me. So we know that telomeres are important.

But it's this question of when DNA methylation clocks came around. All of a sudden everybody just abandoned telomeres as if they're no longer important.

And to your point, which telomere length would you rather have?

Telomeres, Immune Aging, and Senescence

I think they're still important. I think there's still, you know, mean something. And when people are born, people are born just like they have a different, physical height.

They can have different telomere lengths. Right. So some people were more gifted. Some people were less gifted. But then we know that people that have severe limitations in their telomere, lengths, you know, progeria being a classic disease, those people age much more quickly.

And they have, you know, really in their 20s, they developed a kind of age related diseases. People live in their

70s. So this telomere equation, I've always felt has been an important thing.

We've continued to test it, kind of right along. So and I know you've kind of done that as well. Talk to us a little bit about the interplay between telomeres and the immune system, because immuno senescence, you know, is really one of the key, I think, drivers in terms of why people die.

In other words, this is when your immune system can no longer respond to a new threat. Let's say it's Covid or a cancer cell that shows up or whatever it might be.

Yeah. So I just wanna make a couple points. You made some good points. I wish elaborate on them just a little bit here. First of all, telomere length is highly heritable.

It's about 70% heritable. Yeah. So you know, as I say, choose your parents wisely when it comes to the telomere length because, it is one of the you know, it's not like Huntington's disease, but it is quite, quite heritable.

The other point that I wanted to make about telomere length is that it's not to limited length itself because of that high heritability component where you can, you know, I've got patients to come in the average children.

Let's give some other factors. Average children like at a young adult, is somewhere between 8000 and 12,000 killer bases. You know, averaging somewhere around between yeah, around there, around 8000. Okay.

So you lose some from birth to to young adulthood. But you can there's a range of about four killer bases, so that when you're 20, you can have the the killer likes of a six year old, just from what you inherited versus somebody who inherited longer telomeres.

So that's what makes it not such a great biomarker for predicting chronological age, but what it is. And then we talk about species lifespan. Mice have very long telomeres, other organisms that live much less than we do, much fewer years.

And we do have longer telomeres. But if you look at telomere attrition rate, how fast you're losing telomeres, a very nice paper by Maria Blasco looked at that in nine species and found that telomere length attrition rate correlates very highly with species lifespan.

And that's what I tell my patients. Yes, a single telomere length measurement will tell you sort of what you got genetically inherited. And then also what are the things that happened to you that made your telomere length get shorter?

Up until your current yield or like it was measured. But, you know, it is it is really what happens going forward. But you want to look at and so what I do is I traffic longitudinally, I want to make sure that you don't lose telomere length at a faster rate, as you might or even potentially add telomere length or, and that's sort of in that regard, I think it's a it's a very good biomarker of aging.

If you look at telomere length attrition loss over time, which is about 50 base pairs per year, or 0.05 kilo bases per year in, in subjects. Yeah. You know what's interesting?

And we do the same thing in our practice. We measure it and continue to follow it so we can see if people have accelerated aging telomere quickly or whether or not we're actually sort of reversing the aging process for them, sort of telomere play again.

And I think it's useful. And for us, what's interesting is does seem to correlate with, immune system senescence. I think you've seen that. And you want to talk a little bit more about that. Yeah.

So let me talk about that. I mean, remember we're measuring telomere length in white blood cells, right? And the immune system is white blood cells. I mean, the cellular portion of it, aside from lymph nodes, etc..

So when you're looking at someone's color, like now there is a pretty good correlation between telomere length in white blood cells and in other organ tissues, just to make that clear, so that it's not like it's completely different.

But the reason, one of the reasons the correlation between immune system health and aging and here are like this. Because when you're color length of your white blood cells get to short particular lymphocytes.

That is when the cells become senescent, as you mentioned before, can no longer divide, but aren't sitting there quietly being sort of, you know, they don't die, they don't get taken care of like Apatosaurus.

What they do is they sit there and secrete a lot of inflammatory cytokines that you're talking about. That then increases the potential of their neighbors to become senescent as well.

Now, the thing about the immune system is it's one of its main jobs. We all know its job is to fight off infection and tumor. Break the cleaning up of dead and degenerating cells.

That's right. All in all organs. So the immune system is sort of the queen, really, of the agent working depending on what point of view you want to take on it.

I'm not going to be going to be sexist about it. And a very interesting paper looked at that relationship and showed it very, very starkly, which was they knocked out the gene in white blood cells called RCC that is involved in DNA repair, but only in the immune system, not in the rest of the tissues in these in these mouse models, what they found was that even though it was just the immune system that had the gene knocked out for DNA repair, the rest of the organism age much more rapidly, even though they had normal DNA repair in it, because immune system wasn't there to do its job.

And so that's a very stark, example of how the immune system really orchestrates the aging process.

Measuring Immune Status and Telomerase Effects

So just just so the audience understands this and I'm going to I'm going to echo that back to you for a second. Correct me if I'm wrong, but, you know, when you when when you develop senescent cells in any tissue, right.

Whether it's your muscle or, you know, your heart muscle or the liver or wherever, it's really the job of the immune system to go into natural killer cells, to go in there and actually remove those senescent cells.

And that keeps a balance. And one of the things that that happens as people ages accumulate a higher percentage of cells being senescent and in that secretory state.

So that's kind of accelerating. And so you have this buildup of these cells. And then you have this decreased ability of the immune system to remove them.

And you can sort of start to see how this is really accelerating the aging process. So having a healthy immune system becomes absolutely critical. And you know, in our practice we've been able to use a test from UCLA.

I believe you're and use the same thing and maybe some others as well. But this test from UCLA that basically will characterize, the status of the immune system, I call it an anatomical look at the immune system.

It's not a functional assessment, but it's an anatomical look. And then really, if you if we've had success like this, and I'm sure you have too, but it's exciting because if you give people, you know, telomerase activating agents, which is the enzyme that can re lengthen telomeres, you can actually see these immune systems go from senescent to not being senescent.

And that's super exciting to me. Yeah. So that UCLA panel is panel that we developed initially back in 2007 when we did the initial cohort that went through my practice looking at the effect of the telomerase activator that you're mentioning to 65 on, on healthy aging individuals, and it consists of looking at, T cells, naive T cells, and

particularly senescent cells as measured from a cellular level as whether they are expressing this marker Cd28 or not expressing CS 120 I assume you're talking about the same one.

It's yeah. And so so yeah, what which you can see is and what we published in subsequent papers. A randomized control trial is that when you turn on telomerase, you get, a reduction in senescent cells.

At about 20% in that, in that, in that study. But I see in my practice that if you go on for longer than a year, two years, you can have some places where you have as much as 50% reduction in the suggested cells, as defined by lack of expression of that CD 28.

And that's not just sort of like gray hair that molecule is what allows the cells to briskly proliferate and fight off whatever infection, tumor, molecular snip it.

It's uniquely designed to to fight off, you know, very, you know, robust way. If you don't have that, you can't do that. And in fact, when you don't have that, you also have less telomerase activation.

There's altered metabolism of the cell and then it starts to produce that inflammatory, secretory phenotype called the sass that you're talking about.

So we have seen, yes, the reduction in those and actually an increase in the naive T cells, the ones that are they have not found the molecular snippets are supposed to fight off and are available to fight off new infections in tumors.

But by doing that, which is really, pretty, pretty rejuvenating, I think. Exactly. Yeah. We've seen exactly the same thing. So if you're listening to this and you're wondering what we're talking about, you know, many of you have heard about DNA methylation tests and you can check that in the urine.

You can check it in the blood. The people at True Age have developed a, protocol that looks at a number of different parameters related to DNA methylation ages.

They now have a symphony age where they can go in and give you a DNA methylation age, or at least estimate it for about 11 different organ systems, which is useful.

And they can also give you a rate of aging. All of that is very useful, but I think you'd be remiss to not actually measure your telomeres and actually understand where are you in this in this game of telomere shortening and also understand what's the status for your immune system.

Right. The DNA methylation testing will estimated in the past, although it's not on their current report. But we found that when we actually measured it, we got better results in what was estimated from the DNA methylation pattern.

So if you're thinking how do I optimize this part of my longevity strategy. Yes. Do the DNA methylation, but don't think that that's the only thing that you need.

I still think you really need to know what your telomeres stand, where your immune system stands. So yeah, I 100% agree with you. I think that, DNA methylation is a really exciting technology.

And it's and I think moving away from the first generation clocks to the second and even the third generation clocks is, is really, a very good move forward clinically.

But predicting telomere length or immune cell subsets, which actually we, we submitted, we shared data with two diagnostics from our practice in the UCLA, test to help them come up with those predictions.

You know, they're they're good. But I think seeing what I see in my practice is the effect. And I haven't tracked it as closely as their, their T cell subsets that are predicting.

But I think you're right. You want to actually measure the flow cytometry, which is what this UCLA panel is. To see the actual subsets themselves within each individual.

And then telomere length, of course. Well, they can't predict it. And I have talked to, you know, Ryan Smith about it. And I think it is, a really interesting that they can predict and they can be pretty close in their predictions.

And there is this idea that predicting the way in which they predict it predicts better some of the outcomes that might be related to telomere length, I think that still need some more, or some more science to kind of to solidify that claim.

Lifestyle, Stress, and Telomere Attrition

But but the, you know, I want to get back to, just one, one, one point that you made earlier, which was a very good point about people with really short telomeres, the short tailor syndromes, what they call interior biology disorders, CBDs.

Progeria is one of them. But I think it's a really good example of why, when people say, you know, your children aren't that important for you, if you have one of these 200 biology disorders, you either lack you can like 50% of your telomerase activity because of a genetic mutation that you inherited from your from your parent.

And even with just 50% loss of that activity, your telomeres are much shorter at birth. And they get shorter, much faster. And the second and third generation of people that have had that mutation, they don't make it past 10 or 12 years old, because of a lack of enough reserve for their telomeres, the first generation, they often die of pulmonary fibrosis or bone marrow, dysfunction, aplastic anemia, because they aren't quite as sure.

But in fact, the next generation, they've inherited a short telomeres from them and they have only 50% telomerase. They get shorter telomeres. And the disease is called genetic anticipation, where the disease gets earlier and worse and different in this presentation, with each generation after the third generation, they don't make it out of the uterus.

Right. So, you know, when somebody says YouTuber like, doesn't matter. That's why I showed them that example. Yeah, it's fact is really what you're saying, right?

It's compounded through that series of generations, so to speak. Right. So each generation gets it worse than the other. Yeah. No. And we haven't taken care of folks like that.

But, but we know it's out there and it's another, I think, really strong reminder just how important telomeres are. Right. You do you don't want to get into that particular situation with your own telomeres and being short.

Do you want to talk a little bit about some of the lifestyle choices that that shortened telomeres for people and maybe some of the impact of Covid? Just so people are aware of some of that?

Sure. What I love about pure biology is and cylinder length as a measurement is that everything that we know that is good for you from a lifestyle, diet, exercise, even drug therapy standpoint is associated in many studies.

There's thousands of studies now on telomere length. Association with multiple parameters is associated with. Telomeres. It doesn't it's not necessarily that exercising and eating a healthy diet, getting enough sunlight to get vitamin D or taking vitamin D is going to lengthen your teeth, but you're going to have a slower attrition rate, which again, remember that's what's associated with lifespan species.

Conversely, everything that we know is associated with bad habits like smoking, being sedentary, being overweight, being overly stressed is associated with more rapid telomere like shortening.

And there's molecular mechanisms for that. For instance stress. What is stress cause your to investigate. Sure. Well cortisol which is increasing stress is a telomerase inhibitor.

It turns down the enzyme somewhat. So you get more you get less like for you know, telomerase activity because you have more cortisol. So it's really a great integrator of multiple things that you're doing to get an idea about, like, I like to say, all this slings and arrows that your body has had to, had to, withstand over the years.

That's what is integrated in your lymphocyte telomere length. I should say something about two about like measurement. There are a number of companies that use them.

There are, and they all do a reasonable job. But the company I like to use is called repeat diagnostics because they measure both your lymphocyte telomere length and your granule circular length.

It's like, is the cell that goes on to become a neutrophil, and it is released for the bone marrow circulates for a day and then doesn't divide again.

But so that is a good proxy for your. So one of the things that is interesting about this is that when you are having those bad lifestyle choices smoking, sedentary, lifestyle, high insulin, you know, insulin resistance, things of that nature, you're actually increasing inflammation and oxidative stress.

And when senescent cells kick in, they also with the secretory phase increase inflammation and oxidative stress. And it's possible to actually measure the DNA damage that's being done by that oxidative stress.

We have markers for that, in the blood work that we do, through Genova actually. And whether or not, mirrors are being attacked, if you will, by this inflammation and oxidative stress.

COVID, Long Haul Effects, and Final Takeaways

So to Doctor Raphael's point, the fact that you're inhibiting telomerase. So now you can't re lengthen them, but also you're accelerating their demise through this inflammation and oxidative stress.

And that becomes, a really critical part of the story. So the other thing is that we know that meditation, and learning to meditate and really gaining perspective on life to where you're, you're not really struggling over the details, but you're kind of rest at peace and kind of a higher psycho spiritual space.

Really takes a lot of pressure off your biology, and it decreases inflammation. It's associated with increased telomerase activity, increased telomere length.

It also is associated with improved DNA methylation age. So that kind of psycho spiritual approach where we focus so much on the biochemical approach, but that sort of understanding that that psycho spiritual space is so critical, it will move the meter on many, many, many different metrics of measuring in the aging process.

And I think if you'll take this to heart, we've been, impressed with the ability of re lengthening telomeres to revitalize the immune system. We've used to 65 to do that.

There are other things out there like Tammy 818 which can also have an impact on this. And so you can look into these things. But I think, where you would start would be to do a DNA methylation test and at the same time do a telomere test and do a UCLA test to look at your immune system.

This would be a nice triad of testing that you could do to kind of put this together for yourself. So Doctor Rafael had a little bit of a technical difficulty and, departed the, the show here a minute ago, but I just wanted to give you that sort of synopsis.

In summary, I will say this to about Covid and with regards to long haul Covid and that is that what we noticed is that there's two things going on here.

One, people that had, short telomeres were ones that ended up in the ICU and died. And in other words, it was also indicative of the fact that their immune systems couldn't modulate themselves properly.

They ended up with excess inflammation that couldn't be calmed by normal immune system. And then the flip side of it is that people that got Covid and survived it also shortened their telomeres.

And you should understand that telomere lengths are dynamic. They go up and down. It's not just a linear line like as you go through life, they're always going to get shorter.

For example, if you go through a stressful period, your telomeres may get shorter. You get into a very, abundant period or a different mindset. Your telomeres will re lengthen.

If a woman carries a child and is pregnant, her telomeres will shorten and she'll age. And then afterwards she'll regain, telomere length. So these things are very dynamic.

And part of the people that have long haul Covid and sort of persist in immune issues. One of the things to look at there is what the length of their telomeres are.

Maybe that's a piece that also needs to be addressed, as well as addressing their decreased energy production through mitochondrial interventions. So I just wanted to, let you know, the telomeres, even though people think that, well, it's all about DNA, DNA methylation.

It's really not telomere length is alive and well. It should be addressed. It should be looked at, they should be taken care of. And I think when you do that, you're going to find that you really do a lot to optimize your your longevity and your potential for a lifetime.