TELOMERE SUMMIT

Telomeres in a peak performance practice: Practical questions answered on measurment and dosing.

Dr. Joseph M. Raffaele, M.D.
Dr. Sanjeev Goel

Dr. Joseph M. Raffaele, M.D.
Welcome to another episode of the Telomere Summit. I'm your host, Dr. Joseph Raffaele. Today, I have the pleasure of speaking with an esteem clinical colleague, Dr. Sanjeev Goel. Dr. Goel is a medical physician and founder of Peak Human Labs. His mission is to disseminate knowledge of the latest cutting edge medical tools and science to help more people live in a peak mental, physical, and spiritual state. You can learn more about Dr. Goel at longevity.peakhuman.ca. Welcome Sanjeev.

Dr. Sanjeev Goel
Welcome. Thank you so much for having me. I'm really... I think I'm quite honored to be on the summit and quite amazing cast of interviewees you have, so thanks again.

Dr. Joseph M. Raffaele, M.D.
It's great to talk to you. I know we were catching up a little bit at the AFRM meeting about things that are happening in the field, but what I'm really interested in is sort of hearing about what your journey is, how you got to the practice that you have at Peak Human and know where your passion lies in this field. And then we'll talk a little bit about your approach to aging and your experience to the clinical application of human biology.

Dr. Sanjeev Goel
Sure, sure. Yeah. So I'm a family physician trained in Canada and have been practicing for about 25 years now. I've always been interested in things that are, I guess, non-traditional in medicine and have been going AFRM meetings for at least 15 years. But about four years ago, I ran we call it a Biohack Summit in Toronto. It was in person and I brought a lot of speakers in to talk about things that are just a little bit on the outside of medicine, including hyperbarics and

psychedelics, and functional medicines experts and so on and so forth. And that really led me to start Peak Human. And then the journey has really moved into the longevity space because of... Really, I myself am just over 50 now. So I think you start to do the things that really matter to you and for your own health, and then I started doing that and then I realized, "Oh my God, there's so many people like me who this is a really important thing to do with, which is aging." And that's how I've now focused my practice on with. That's what really Peak Human's about.

Dr. Joseph M. Raffaele, M.D.
Well, first of all, you don't look anything like 50. So that's pretty. You're doing something absolutely correctly besides choosing your parents well, of course.

Dr. Sanjeev Goel
That's

Dr. Joseph M. Raffaele, M.D.
As they say, but yeah, that is a story that you do hear that once you start hearing about all this information that's out there and you see you and I both probably had really pretty good health for a long time. And then I've been in the field like 25 years, but you just start at some point, you start saying, "Hmm. I'm starting to feel a little bit less well than I did even though I don't have any diseases, not sick of any chronic medical conditions." What is there that you can do? And there's just a whole lot that you can do. And tell me about the kinds of things you do in your practice, what your assessment is, what your philosophy is around it? It's all encompassing certainly almost like the World Health Organization, and true health is a state, not just an absence of disease, but a spiritual, mental, and physical wellbeing. Tell me more about that.

Dr. Sanjeev Goel
Yeah. Family medicine has that route anyways where we're trying to look at a personal and a holistic manner, but the problem is that we only get like five minutes-

Dr. Joseph M. Raffaele, M.D.
That's right.

Dr. Sanjeev Goel
In the government to paid system here in Canada. But so obviously we look at the patient, we spend some time to understand, what their goals are, what are the current issues, what's happening in their lives from a bio-psychosocial model. But I think what I like about what we're trying to do with Peak Human is that we're trying to add some, we call it like science behind it some data, and that's everything we try to do pretty concept, comprehensive blood work,

beyond the usual things that your doctor might order. And I started ordering the Epigenetic Age Testing from TruDiagnostic. That really began with some of the thinking about, "Okay, what could we do beyond that?" I do a GlycanAge on everyone now. And I've been doing these days, something called the GlycoCheck, which is like microvascular score looking at it at the time. And then we're now doing also some brain EEG recordings through the wavy. So we're still early in understanding how do these things look longitudinally? But that initial assessment, we're trying to make it as comprehensive possible. Even as someone who's looking healthy, we're trying to see if we can have something, some true biomarkers that we can then follow that are really preclinical before any actual disease happens. We can tell people, "Hey, this is what's happening from the effects of the lifestyle trip interventions or other interventions we're prescribing." Cause that's always been the limitation I felt with this type of medicine is that we could tell somebody something, but I could never prove to them that I was actually making a difference. And so that is still like the holy grail for me, so just how can we prove that, let's say someone's doing an exosome infusion or taking rapamycin or whatever? How is that really impacting their system? So that's what right now we're doing at peak human.

Dr. Joseph M. Raffaele, M.D.
Yeah, it's kind of funny you use the term preclinical, which we all just kind of rolls off our tongues because it's the natural way of thinking about things, but, it really is shows that medicine is focused on disease and you don't even call it clinical until you actually have a disease, whereas with these biomarkers that you're talking about, there are well-documented changes year after year of a loss of one to 2%, 0.5% in some that is adds up over the decades even before you're diagnosed with anything. And that's also been shown that in most things and particularly in cardiovascular disease that looking at and making changes at that point is when you can really do something. Once the stress test is positive, the horse is out of the barn. You're gonna be having an angioplasty or you're gonna be having bile bypass surgery at some point, or something else is gonna kill you. So I think that for me, has been sort of the holy grail has been, how do you measure the effect of these things at the "Preclinical level." To tell patients who come in... My patients I'm sure like your patients are like, "What about this? What about this? Should I try this? A friend of mine is taking this." I'm like, "Well, how do you know it's working? And how do you know what's the right dose in human?" And in other things like high blood pressure, which is sort of a preclinical thing really, if you think about it, it's asymptomatic, there's no disease there until it gets really high. You just wanna make sure that what you're treating with is actually working. And that's what these other markers are about, which I think is really kind of interesting. So in your practice then, I guess you're thinking about health more than disease. You're thinking about aging as a prodrome to disease. Tell me a little bit about your thoughts we were talking about that before we started recording.

Dr. Sanjeev Goel
Yeah. I just jumped shot, I want to jump in that the other thing that in the biohacking space where I really started from this idea that we should give people as much access and an understanding of their own data. So I'm really a big proponent of wearables, like things like the Aura Ring, and I've been wearing an Aura Ring now for three years straight. And I've seen the amount of little variation that only I could understand that, and no doctor couldn't really understand a little minor, like a four point change in my resting heart rate. I can notice that, "Okay, there's something that's different about today than there is about another day.

Dr. Joseph M. Raffaele, M.D.
Sure.

Dr. Sanjeev Goel
So I think that type of stuff, I think it's pretty exciting. And I think it's good for medicine to be involved in that rather than it bypassing us. Like that's what probably could happen if we don't be involved in this whole field of the data that's coming from wearables.

Dr. Joseph M. Raffaele, M.D.
Yeah. So how would you sort of situate biohacking in sort of a space of longevity medicine or age management medicine? The doctor and patient relationship? That term biohacking has been out there for a while, and I think, I guess it means sort of more day to day personalized kind of things that work in a sort of and of one, you are the one that it matters that you see what the results are of things, but when you're... You've worked with a lot of biohackers, and how do you do that as a physician prescribing and certain things that you have the ability to prescribe but they don't? Although some biohackers are pretty resourceful.

Dr. Sanjeev Goel
That's true. Yeah. I take it a guess, it's an ends of one, but obviously informed by other ends of one, like we can give a potential suggestions based on what other hackers are doing, but I call them enlightened health citizens, like people who are biohackers are not really... And in fact we should all probably become biohackers in effect because I think it's the ideas that we want to, but there's everyone's has their own responsibility and should have their own, we call it autonomy to get that data and then make decisions on it, because they're probably be the best at it comparatively than someone else.

Dr. Joseph M. Raffaele, M.D.
Well, there's certainly the ones that care the most about it although, we care about our patients, but in the end you're... And I agree with you I think at some point, not even at some point having access to that kind of data is important. So I think having... And that's part of what I've been doing with my software and the PhisioAge Software, trying to give patients as much access to their longitudinal data over time to see how interventions are affecting them. We have not yet added wearable data, but we will at some point, because we have sort of longer term tests, like capable of an A1C and telomere length and senescence, et cetera, markers that they wouldn't necessarily get from a wearable, but things like blood pressure we know, and certainly central arterial pressure, that's gonna be most important to learn on a day to day averaged over time kind of thing not just once every quarter when they come into the office. And that's why I actually, one of the technologies I use in my office Vicoder, or now it's called a cardiacs arterial stiffness device is gonna be wearable fairly soon. So you can see today what your central arterial pressure is. Maybe you should take a little easier if it's a little high, maybe worked out too hard yesterday, akin to looking at your heart rate variability kind of thing.

Dr. Sanjeev Goel
What do you think about... I saw this at the conference about the device, which looking just through pulse take and determine your arterial elasticity. And do you think that ?

Dr. Joseph M. Raffaele, M.D.
Yeah, those devices of that type have been around for awhile, it's called digital plethysmography, which is a little light that looks at your capillary pulse, and gives something akin to the wave form, which is a pulse wave analysis, kind of looks like an EKG of the blood pressure cycle. It can give an approximation of that to the one we get with a bigger fancier machine here. And it's legitimate. It's helpful. You can get an idea about what your sort of pulse tracing looks like relative to someone else your age. Only problem with those is that sort of the temperature in the room is a little bit more important cause the peripheral circulation can be tamped down a little bit, but they're pretty good devices. And certainly for biohacking purposes, they're gonna be pretty good because you can just put them on whenever you want to. But like I said the same technology that's being used in my office with the SignalCore is gonna be available fairly soon. It's already available as an ambulatory blood pressure instrument. Ambulatory central arterial pressure through a doctor's office, but potentially very soon as a wearable for the biohacking community and anybody else that wants to use it. And we can suggest to our patients to use it and then upload it to something, not necessarily our the traditional VHR, but I think you're right, the more data the better.

Dr. Sanjeev Goel
Yeah. Thanks for helping with that. I wasn't sure that's a worthwhile instrument to add to my-

Dr. Joseph M. Raffaele, M.D.
I think so. It depends on which one, but also... And I'm not familiar with the latest ones, and it's also considered the most expensive instrument that I have, which is $67,000 now. But it used to be 20,000 when they were sold primarily for pharmaceutical companies. So they've come down quite a bit in price. Yeah. So you initially you get all that work on your patients and then you do work in looking at their aging process, but when you look at them.

Dr. Sanjeev Goel
Yeah, so generally, as you know these results come back, let's say that, I have ordered telomeres. I forgot to mention that, I do order telomere testing, but not as much as I used to to be completely honest. And a bit, the concern of that was to be I was ordering from a company called LifeLinks in Spain. I was finding that there's a huge variability. It didn't seem like we had the results kind of matched, but I did do some sequential, some mystic bunch of blood tests as well on people. But from what I was reading, I was hearing that the precision wasn't so good with this type of testing. And so I've kind of held back from doing that type of testing.

Dr. Joseph M. Raffaele, M.D.
Yeah. So I think that what I do hear that and I read that in papers, and I think that there is still work to be done on a general consensus. There are different technologies that are used for telomere length measurement, there's Flow Fish, there's PCR, there's high flufloid, they're quantitative Flow Fish. So I think what I would say is that if you're using a company, you stick with one company, and follow them longitudinally. The other thing I would say is that, the coefficient of variation on a telomere length measurement isn't that far off of both within the asset is the same sample and measure a few times. It ranges from two to 3% for Flow Fish up to five to 10% for PCR. The two to three is not that far off for cholesterol measurements or any routine chemistry, CBCs, et cetera. There is biological variability though, which is pretty important to keep in mind and people sometimes, I've talked to other clinicians that have lost faith in them because they're like, "Well, this is one year or six months to pass, and there's now a six year difference in their telomere length. And what's this all about?" Well, the biological variability is quite significant. So you have to get a number of telomere lengths before you get an idea about what the trend is particularly. So if you have say six kilobases about average for a 60-year-old, but if you have two to three, even 5% variability, you can have a few years of variation just test to test. Now, and I see that in my patient, I've been measuring telomere

length for 14 years in patients, and I'll see them at 6.5, 6.4, 6.7, 6.3. And LC1 is at 5.8 and that's weird. Is that because they've really lost telomere life? I don't think so. I think it's because the percentage of senescent cells in their circulation on that day was a lot higher. The senescent cells have much shorter telomeres. So the average is coming down. You have to remember that when you're measuring telomere length in a sample of white blood cell sample, it's a lot of different types of white blood cells from naive T cells to B cells to natural killer cells. Depending on if you're using like Repeat Diagnostics, you'll also get granular sites, which are neutrophils, which their telomere length don't get shorter once they're in the circulation. So you have to keep in mind what the technology is that you're using to measure it. All that being said, I would say that measuring them over time, you can get the information you need. You just have to interpret correctly. There's something called pseudo telomere lengthening and shortening. And that kind of is based on the cell population on an actual change in telomere length, like the composition of cells that you're getting at that sample on that day. So just that in mind when you're pressuring them. I encourage you to start measuring again -

Dr. Sanjeev Goel
Yeah, you're... Yeah.

Dr. Joseph M. Raffaele, M.D.
because I think they're important to to know.

Dr. Sanjeev Goel
Oh, sorry. So You're saying that by infections like someone can have infection that could change, like what causes a biological variability? Are you saying stress? There's .

Dr. Joseph M. Raffaele, M.D.
Exactly. So if you have exhaustive or even fairly moderate exercise the day of the test, it's one of the benefits of exercise it mobilizes the senescent T-cells from the tissues into the vasculature to be removed. But that's going to change your composition, so that there's going to be a heavier weight towards shorter telomeres, and your median telomere length and what's getting reported out is shorter. And even if you're using like lifelines and they're looking at median telomere length and 20th percentile, bottom 20 percentile, well, 20th percentile might go up because there's more cells that have shorter telomeres, and go down, sorry. The length of it goes down, and that's not actual change in telomere length. So if a patient has exercise that they're always encouraged, not encourage them, just tell them not to exercise the morning of the test, before they come in to get the blood drawn, or if they've had heavy alcohol intake , or really bad night's sleep, or after jet lag, or certainly if that any inflammatory process going on, even a mild cold or an infection of any kind post-surgically, don't measure those tests under

those circumstances. You're not gonna get the information that's telling you about the sort of more stable state that the patient normally is in. So it's important to have all those caveats when you're measuring these things. And that's also true for any time you're looking at senescent cell measurements of the various kinds of their available.

Dr. Sanjeev Goel
What's your thoughts on... I understand that there's a methylation test that can basically also measure telomere length. That'd be genetic methylation test that seems to be apparently more accurate than actual telomere.

Dr. Joseph M. Raffaele, M.D.
Well, so it depends how you define accurate. That test is used by the same company, TruDiagnostics. It's a prediction of telomere length based on DNA methylation patterns that are more accurate for certain other outcomes of telomeres, not actual telomere length. The actual telomere length is... And I get TruDiagnostics tests often in tandem with... And they can be accurate, but they can be... I have to assume that the actual test itself is the gold standard, right? It's like these genome-wide association studies where they say that they predict better than the actual marker that you're looking at. That depends on what you mean by better and more accurately, if you're actually looking at want to see what the actual length of your telomeres are, you measure your telomeres. You can get a good approximation, and it's very interesting and we're working with the company to hopefully improve their ability to do that, so that they can really come up with something that perhaps could replace telomere lengths, but I don't see that happening. It's not the same as predicting chronological age. So I think it's interesting information to have. They're looking at it to also to predict senescent cells. So I think that there's definitely gonna be some progress made in that area, but for now I would actually measure the telomere, it's the actual data that you want. If you can use some other cheaper, or another way where you're getting other information, then at the same time, and you have limited budget, then sure. That may be a good way to screen for somebody who has extremely short telomere lengths. Although I don't know how accurate it performs under those circumstances. So you've measured some telomere lengths, have you ever come across anybody with really long telomeres or really short telomeres?

Dr. Sanjeev Goel
To be honest, no not really. And no, it's been pretty much right in the middle there, but I was curious about, I've been using TA-65. I've used it probably for eight years.

Dr. Joseph M. Raffaele, M.D.
Oh, really wow.

Dr. Sanjeev Goel
I stopped for about four years or so. But I think before the randomized trial came out that showed that there was actually length in telomeres, because before that, I was kind of waiting for the research to kind of be a catch up for that, but I'm using it now and I'm recommending to patients, but I haven't been able to follow up test to see if there's change yet in my patients.

Dr. Joseph M. Raffaele, M.D.
But you're right there in Canada with Repeat Diagnostics just to left or right depending which way you're facing.

Dr. Sanjeev Goel
Yeah, exactly.

Dr. Joseph M. Raffaele, M.D.
Over in Vancouver.

Dr. Sanjeev Goel
Yeah.

Dr. Joseph M. Raffaele, M.D.
And their testing is I think really quite accurate, and useful. I know I've looked at probably this point over 2000 telomere length tests with them. We have data that we collect and it's... I'm always amazed at how well, the data that we collect on our patients matches the published data in terms of lengths and average length and spread and that kind of stuff, so that clinical research, which is fun when you have time for it, I've been trying to do a fair amount of it, it's really gratifying to see that. So, yeah. So perhaps think about it again. And if you use PhysioAge, which I'm gonna get you on I think at some point, you get $100 discount on it. So pretty much pays for the software if you do want telomere length measurement per month, then you're good, because when we get a pretty good discount from them. So Peak Human, how would you define that? What are you looking to with that? And so you're looking at a holistic cause you're going from family practice to what you think family practice ought to be just like I went from internal medicine thinking what internal medicine ought to be. And so what are the kinds of things that you think our listeners might want to hear about it that you do that perhaps other practices don't do?

Dr. Sanjeev Goel
Yeah, let me think about that. What we try to do is again, get patients' understanding of what their labs are like, so they actually take ownership of that. And then I am recommending now certain patients take metformin, rapamycin. We are putting patients on some protocols on that. So everything that we're trying to keep it evidence-based, science-based, but these are for patients who are relatively, still feeling pretty healthy. So we wanna basically prevent onset of a disease as much as long as possible, we can do that. Again, it's a relatively new practice. It's only been about two years since we've had most of our patients come on, it's kind of early days to see, but I think just the fact that patients have an option, I think that's what's they're really excited about. There isn't too much here in Canada that really has this type of option for them.

Dr. Joseph M. Raffaele, M.D.
Yeah. It's great that you're offering that. So they can have a more comprehensive look. I think patients are taking with the advent of PubMed being available and then all this advertising on social media of information in the longevity field, which is just exploding, really just the amount of information that's available. Some of it is clinically actionable in terms of taking molecules, whether it be you TA-65, or glutaral, or gluthatione or something like that. patients are like, "So I try this, I try that, so I try this." But they need to be guided unless they're like really experienced biohackers, in which case they're probably on Instagram, giving out their information to people. The patients need to be guided as to what is something that actually is working in them. And metformin's a great example. I'm all for the team trial. I was talking to I think one of our other speakers about, and I think that metformin has great data in a certain patient patient population, which is probably not yours or my patient population. Most of my patients are exercising at fairly close to their ideal body weight.

Don't have a lot of insulin resistance, and there isn't any data to show that metformin is going to necessarily have the same reduction in mortality and onset of chronic diseases that all the data sets that are talked about show, that's the average person in the developed Western society. And there is good data showing that metformin can cause a decrease in your response to aerobic and resistance exercise. So if your patients have a hemoglobin A1C of 5.0, I don't know what units you use over there, do you use the IFFC or IFCC, but that's really low and really good. And they're exercising. I'm not on metformin for that reason because I don't think it's necessarily an that that's possible it could have some off target effects. I'll use something like berberine instead, or maybe even GoucodOX, which is a G-L-U-C-O-D-O-X, which is a Gugulipid MCT that has some effect on AMPK upregulating it. But that's I think the end of one, the biohacking part of it, but I'll say, what do you think about this? It depends on the population,

and then it ultimately depends on the effect and that's where you're right. You wanna measure at baseline, and you wanna measure later, is it actually working in memp. That's another reason why I talk about it with TA-65 or any telomerase activator, because they're usually not very inexpensive. There may be a dose, or 100 units. In our study in senescent cells, 100 units had an effect, but that may work in one patient, but because of the differences in bioavailability, it might be 250, it might be 500, it might 1,000 units. You don't wanna waste your money, if 100 is working and you don't wanna waste your money, if 100 is not working. You wanna go to 250 or 500 or whatever you need to go to. And with the telomeres, while people do talk about anecdotal stuff. I don't know if any of your patients have mentioned that perhaps they feel a bit more energy, perhaps they feel it and their vision looks a little bit better. And I've had Tom Dalen who was an ophthalmologist, and he published a study on the effects on macular degeneration of TA-65. So there's definitely mechanisms for which vision might improve. You don't know unless you objectively measure it.

Dr. Sanjeev Goel
And that's the issue. I didn't want to say, "Hey, yeah." Because people are saying, "Hey." Potentially other getting more energy and all that. But it's very hard to say that because again, you have a bias. And -

Dr. Joseph M. Raffaele, M.D.
Yeah, sure. It's possible point in effect. yeah.

Dr. Sanjeev Goel
Yeah, so that's why I think we need probably more long-term data. That's why I think the clinical, the biomarkers are so important. If we can see changes on that then I'm more excited about those results.

Dr. Joseph M. Raffaele, M.D.
So you're using rapamycin or using exercise, prescription and diet and exercise, that sort of thing.

Dr. Sanjeev Goel
Yeah, a lot of... Again, I probably even mentioned this that I really come from interest in impact of diet on health. Did quite a bit of reading in the whole space on fasting, which I do recommend to patients. I recommend the fast mimicking diet as well. The ProLon, done four cycles myself in the past year or so. But yeah, I'm a big believer and that's important for the body that one needs to probably take a break from food and whether that could be also keto potentially, I guess. And so I try to also have a lifestyle kind of component to this as well, and for

exercise, yeah. Weight training, I think is critically important. Some high intensity interval training. Those are things I ask my patients to do, but that's a much more, but I think everything is in gradual. Like when people come in, I kind of have to focus on where they're at, and for them, the first person that gets maybe just cutting out soft drinks. And that might be just .

Dr. Joseph M. Raffaele, M.D.
Quitting smokers for patients.

Dr. Sanjeev Goel
Yeah.

Dr. Joseph M. Raffaele, M.D.
I was like, "I'm here for age management, but I'm still smoking." That's problematic.

Dr. Sanjeev Goel
Yeah. That's .

Dr. Joseph M. Raffaele, M.D.
That's a really low hanging fruit. That's actually... It's on the ground.

Dr. Sanjeev Goel
So yes, people don't come in saying, "I'm here." Cause they're all super already knowledgeable, mostly for just some case. "I want to just feel better." And are there like most people like say, they're 50 and they're looking to noticing that something's changing and maybe they need hormones. That's really how this practice started is that people want to come in for hormone replacement, men primarily growth hormone replacements so on and so forth. And it's kind of now moving them along from that, to what I think is true interventions to kind of prolong .

Dr. Joseph M. Raffaele, M.D.
Part of the aging process itself. That's actually the genesis of... Not the genesis, I guess the genesis of my practice was really my starting and starting my parents on growth hormone and other sex hormones. And then back opening the practice up, once the Women's Health Initiative hit, I did and have done and continue to do a lot of hormone optimization. But in the last five to 10 years has been so much on more direct aging process stuff in molecules involved in that. But I've been really heartened to see that all of this stuff that we were doing with hormones prior to the Women's Health Initiative, say calling it an anti-aging medication is being born out with these newer molecular diagnostics. For instance, I had Gordon who is the

founder of the GlycanAge creator of it. And menopause worsens your glycanage, it makes your immunoglobulins IgG more inflammatory, it makes them raise your glycanage. I see in my practice, I put someone on HRT and their glycanage comes back down 10 years or 15 years. So those are important molecules. They're still really important part of the arsenal that we have pre-menopausal, you don't necessarily need it, but in testosterone does the same thing in men. And then same with DNA methylation and epigenetic age. You see that menopause accelerates that, HRT slows that down. So I think it's just been really really interesting to see that these sort of more geroscience markers have validated this stuff. And even growth hormone, which a lot of Valter Longo you talk about with ProLon and intermittent fasting, sorry, at the time mimicking diet and fasting, IGF1 is the bad guy.

Dr. Sanjeev Goel
Right that's true.

Dr. Joseph M. Raffaele, M.D.
It's the one that of course they don't have, and that the Ecuadorian doors don't have. And you're trying to lower IGF1, but the Trim Trial showed that there was an epigenic aging reversal with metformin growth hormone in DHA. So how do you make sense of that? There's still more work to be done as far as I'm concerned.

Dr. Sanjeev Goel
Yes, you don't have a clear opinion on this. I would love to hear your opinion here on the growth hormone piece. You may have much more experience. What do you think on that and longevity? Is it just a fine balance?

Dr. Joseph M. Raffaele, M.D.
Well, yeah. I think, look I do have certainly many years of experience treating patients 25, 24 years or something like that. And I'd been on growth hormone in a long time. I think that the problem is that lower animal models are not good models for looking at the effects of growth hormone. And they've also looked at them in the wrong way. They've looked at them in transgenic models. We know that acromegaly is not good for you.

Dr. Sanjeev Goel
Right.

Dr. Joseph M. Raffaele, M.D.
We know that you've got an IGF on a 5,000, that's not a good thing. In some bodybuilders on stage probably do have an IGF1, of 5,000, but that's not good for their longevity. Their organs are

increasing in size, their hearts increasing in size. But we also know that IGF1 in observational studies is associated with higher cognitive for a performance in older individuals. So I think the story is much more complex that the effect of IGF1 on immune system functioning. There have been studies done looking at giving middle-aged mice or rats growth hormone, and they actually do fine, they actually do a little bit better. That's what we're trying to do in humans. We're not trying to make transgenic humans such as make too much growth hormone, and we know what that is, that's gigantism or acromegaly. So I just think that that's not the right way to think about it in that. I know as clinician that if someone's IGF1 is low below 100 and I bring it up to 150 to 200, which is still in the physiological range, they feel a lot better. They're cognitive. They feel better. Their mood is better. Their energy is better. The body composition certainly improves, their hair grows faster, their nails grow faster. So performance wise and quality of life wise and health span wise, I think that you see benefits.

And that's why one of the reasons growth hormone is still FDA approved for lifelong therapy in growth hormone deficient adults, who are not any different in circulating growth hormone levels from somebody with severe IGF1 deficiency from aging, or from obesity, or from stress, or from lack of sleep. So I think this idea, it's a kin to the whole idea of just wiping out estrogen in women, because that's gonna cause breast cancer. Yes. IGF1 is a mitogenic signal. It does stimulate cells to divide, but now they have large databases following things. If there's an increased risk, it's slight in colon cancer perhaps, but that's in very high levels of growth hormone and acromegaly. I think it's a balance. You wanna walk a balance and you see how the patient responds to it.

And there was also another study that I was interesting we looked at, if you gave growth hormone, there was an increased risk of cancers in these rodents, but if you gave them a great supplement pack that reduced their oxidative stress, that was reduced. And so I always give my patients full supplement regimen to help reduce their oxidative stress. So I think that we have to look a little bit more in a nuanced way at these things before we decide that one molecule is really good, or one molecule is really bad. Even telomere was... There's talk about really long telomeres being problematic. But that running in families that increased risk of gliomas and some other cancers, non squamous cell or adenocarcinoma of the lung, but those are very unusual circumstances. And for most people, I think keeping your own telomere length where it is when you're young, or keeping it from getting shorter is much much better for you. So it's all about the balance, keeping the balance.

Dr. Sanjeev Goel
Do you think the GH... I normally ask my patients to do it for three months, take a one or two months off. Like do you think this may have some benefit that because naturally not everything

is always growing, not everything is always dying? In fact that maybe the body has to go through some type of cycles, it's normal.

Dr. Joseph M. Raffaele, M.D.
The whole cyclical nature things is really interesting. And I've looked at that. I've done that myself gone off of it for periods of time. It's just hard to know, because just as in the growth hormone inefficient in adults there's not a period of time and they're sort of normal. So those studies need to be done. It'd be interesting if they were done. Molecules have different effects with different dosing intervals. That's clearly true of rapamycin, which if you gave it to cancer or immunosuppressant therapy doses every day a couple of milligrams, five milligrams or whatever is much different than five milligrams once a week for eight weeks. So it's possible. I don't know the answer to that, and I don't think anybody does, but I think that we shouldn't dismiss these molecules that are in pretty reasonable abundance at our peak of health and say that we're better off having very low levels of them to age older.

And I don't even think that if you look at a centenary and say, "This is the hormonal ambiguity that you wanna have in order to live a longer life that of a centenarian." That doesn't necessarily make sense to me either, because centenarians, while they're still alive and they may be disease free, they're not performing the way a 25 to 35 or 45-year-old is performing. And that's ultimately the goals to maintain humans at a level of performance that they are at their peak performance for as long as possible. That's my take on it at this point. I think that practices like yours and like mine, that's why I created PhysioAge just to help have data on patients that are getting different regimens, and look at it and see how people are doing. And then using our vast computing power that we have these day to really analyze what is happening in 50, 100, 500 age management longevity practices around the country and around the globe. And then we start to see patterns, maybe in certain individuals.

You don't want to use one therapy, but in other individuals that same therapy has a beneficial effect. It's one thing that I've learned. I don't know if you had this feeling maybe for a little while, but I had it for a little while there, after the Women's Health Initiative came out and all the patients were coming to my practice and we were making them feel better with identical hormone replacement therapy. And I said like, "Well, I know what I'm doing with this now. And I guess, I'm an expert at it. I don't really... What else is there to learn?" Now, I'm just like, "I can't catch up. I can't keep up with all the information that's coming out in aging biology itself." But certainly the biology of aging is super complex. We know some things, I think we're doing some things right. And we don't know some things, a lot of things. I think people are often a little bit too dogmatic about how they think about these things.

Dr. Sanjeev Goel
I'd love to ask you a question, which maybe hopefully yet you haven't talked to with anybody else in the summit. So what's your feeling about CMV infection bias? Do you think how much contribution does it cause the aging?

Dr. Joseph M. Raffaele, M.D.
Yes. Well, that's a good question. We have talked about that somewhat, but I think there's pretty good data on it that... Well, it depends. So there's been a couple of great studies that looked at CMV in older adults, the Cocteau Trial, and the non-A Trial in Sweden, and in healthy-ish like not carrying multiple morbidities and free living 80-year-olds, the CMV positive ones, if they've had it long enough and has had enough of an effect on them to cause an inversion in their CD4 to CD8 ratio, which is normally around 1.5 to 2.5, the helper cells and suppressor cells. If it's under one, so that there's predominance of suppressor cells, that predominance is there because of the accumulation of senescent cells that are focused on CMV and also not dividing anymore, the senescent and they're secreting a lot of inflammatory markers. They have a much higher two, four and six year mortality rate, like 50% higher than those who are CMV negative and have a... Or not... What's called? The immune immune risk phenotype, but that's at the later ends of life.

Dr. Sanjeev Goel
Right.

Dr. Joseph M. Raffaele, M.D.
They then went on to look at 60-year-olds, the Hexa Trial. And they found that while there are some people who are in that immune risk phenotype with the inverted ratio, they don't have the same mortality risk, but there are many other cardiovascular studies, a colleague that's worked on TA-65. I have in the UK, is just finishing up a trial looking at TA-65 in survivors of acute coronary syndrome, either an EMI or sort of angina requiring angioplasty. It was actually an acute AMI you had to get into it. An event was considered one of those things, either a secondary AMI or angina, they're looking at TA-65 to see whether or not it reduces inflammation and potentially second events. So I think CMV is a very important factor in people. It's not a benign virus like we're taught to believe. It's just that's a very long asymptomatic prodrome before it starts to cause problems. And that in some people who is in their 60s with cardiovascular disease or potentially other diseases that haven't been found out yet, because of the increasing inflammation, or it's in their 70s or it's in their 80s where they just overcome from overwhelming infection and die because of their inability to fight it off, because of their

senescent cells. So I think that that it's incredibly important. And there are whole organizations that look at CMV and hold conferences on them. And I think that we could have a vaccination for CMV would probably save more lives. And if we have a COVID, then having a COVID vaccination potentially. More people mean many more people are CMV positive. Well, at this point right now it's probably could be everybody is COVID positive soon. But yeah. I think that I check CMV in all my patients.

Dr. Sanjeev Goel
Yeah, thank you.

Dr. Joseph M. Raffaele, M.D.
I wanna know because I think that if they're in the immune risk phenotype, you need to talk to them about, I think you wanna look at their telomere length, and you wanna think about things that can reduce the senescent T-cells, to reduce that denominator, to improve their chances of having a longer, healthier life. So even if you don't do telomere length testing, I recommend at least screening with a routinely available CD4 to CD8 ratio, and if it's inverted, then do further testing, you can do it that way.

Dr. Sanjeev Goel
Right. I am putting people on one TA-65, if they have a CMV infection in the past, but if they're a little bit older gentlemen.

Dr. Joseph M. Raffaele, M.D.
Yeah. I've only caught one person in all my years doing this, actually converting at a pre and they were CMV negative. I got their senescent cells, they had everything on them, they're asymptomatic. The next time, six months later, they came in and they were CMV positive, and the telomere length was shorter, senescent T-cells have gone way up. It's all been described in the literature that causes a remodeling of your immune system. It's can be up to 10 to 20 years of aging of the immune system. And we caught it, right? It was a snapshot and then longitudinally followed them. He left the practice, I haven't seen him in a while. I'd be curious to know what's... He was a young guy, he was in his late 30s.

Dr. Sanjeev Goel
Oh, wow.

Dr. Joseph M. Raffaele, M.D.
So pretty interesting to see that change over and what it does, and what viruses can do in general to you. And that's where again, I think telomeres are important because it's the reserve

that you have to fight off chronic viral infections, reactivations of them. And the herpes viruses are really in that family of viruses, CMV being the worst, but all the herpes viruses are the gift that keeps on giving. And I say that facetiously because it's not a gift.

Dr. Sanjeev Goel
What can we look forward to in other compounds that length in telomeres, do we have anything else that .

Dr. Joseph M. Raffaele, M.D.
Would it now-

Dr. Sanjeev Goel
Exercise and hyperbaric with that study that came out? Was there anything else that.

Dr. Joseph M. Raffaele, M.D.
Right, yeah. The hyperbaric oxygen therapy study was very interesting, quite a significant telomere length increase and decrease in senescent cells. A little worried about the measurement technique. And I wanna see that study reproduced, but I did talk to Jason Saunders who runs another hyperbaric oxygen therapy company. And they're looking to kind of do that study again, and I've been looking at hyperbaric oxygen therapy for myself. So there was sort of home units that you can have too. I think it was kind of interesting, that we know the mobile ones. But in terms of actual molecules, there are some molecules that Bill Andrews has talked about that are preliminary activators, but there are studies in humans to show that they're in vitro select telomerase activators, that they're absorbed get into your blood and then turn on telomerase and make changes in your telomere length or your senescent cell. So right now it's still that people talk about epitalim being potentially a telomerase activator, and that's possible, but you have to have to do the study. So all the lifestyle diet stuff, I think it's important too and the kind of stuff that you're doing in your practice, I think is important for that.

Dr. Sanjeev Goel
I'm doing some reading that the newborn telomere length is by far the biggest predictor, what's your lifetime telomere would be.

Dr. Joseph M. Raffaele, M.D.
No question about that. The telomere length is 70% heritable, which again, it goes back to the old joke, "Choose your parents wisely." Because and that difference between eight kilobases and 12 kilobases at birth, it's pretty much spread across that.

Dr. Sanjeev Goel
Awesome, yeah.

Dr. Joseph M. Raffaele, M.D.
It is a little more than you're expected to lose over your whole lifespan. So you starting down at the eight, you better not lose it at quite the same rate. And if you're at 12, now you do lose telomere faster the longer it is. That's well well-documented as well. So there's a steeper loss, but you wanna be up there in the higher range, that is true.

Dr. Sanjeev Goel
Apart from your parents' telomere length, is there anything else and intrauterine that could affect telomere length? Do we determine any?

Dr. Joseph M. Raffaele, M.D.
Oh yeah. I think that there's stress that can do that. I can't tell you right off the top of my head and Alyssa Apple, Elizabeth Blackman have talked about that in their book, but I'm sure there are so many factors in uterine that affect telomere length and metabolic health, and so many other things that I'm sure that there's important stuff there. Maybe I'll try this experiment with you for the first time. I haven't done any visuals here. I'm gonna share my screen and, okay put up this interesting plot that we have for people to look at. So let me do this and come over here. Put up.

Dr. Sanjeev Goel
There it is, I see it.

Dr. Joseph M. Raffaele, M.D.
No, you see my screen one, that's your questions.

Dr. Sanjeev Goel
Yes, my questions.

Dr. Joseph M. Raffaele, M.D.
This is what you wanna see.

Dr. Sanjeev Goel
Yeah. I'll seek more it fits. Oh, wow, look at that.

Dr. Joseph M. Raffaele, M.D.
So this is a data from a Repeat Diagnostics, the paper done by Peter Lansdorp in Geraldine Aubert. And we took their dataset, which was available publicly. And I had a data scientist analyze it to look at what was the best fit. You're talking about telomere length as linear decline and say, it's not such a great biomarker that way. Well, it's not actually a linear decline. And the company, when they report out their type of assay, the Flow of Fish Assay does show that there is a steep loss from birth to young adulthood, which makes sense, right? Because you're growing from a fetus. So the newborn baby to a much larger, a lot of cell division has to take place. Telomerase is not active, nearly as much, cause it's turned down significantly at birth. And there's this spread you're talking about, it's about eight kilobases up to 12 kilobases here down to 7.88 to now, if you have a telomeropathy where you have 50% telomerase activity that you've inherited from your parents, you're gonna be down here in the four or five range. And those are known, they're called the telomere biology disorders. But what this my data scientist was able to do was this red line is the instantaneous rate of change of the curve. And this is a specific curve that we fit to this cubic curve. And so you can put in the value, what's average for a 44-year-old? Let's say a 52-year-old, and it'll come up there. I'm sorry. You have to get telomere length here. So telomere length here at eight. The average is 6.1 at 52. And you see this spread. And so if you start out up here and you're going like this, you're gonna be much better off than if you start out here and even have a flatter, because you had a lot of good lifestyle stuff. And that's why this spread is why telomere length is a single biomarker. They say isn't such a great biomarker, but following somebody longitudinally is I think very valuable. And we're gonna have this same plot available in the software fairly soon, so people can look at it. And we give you a Salaam region already, which is what your age is, but to have people know what... And so you can see the rate of loss here is around... The slope is quite significant. At that age say 14, you're losing a 10th of a kilobase.

Dr. Sanjeev Goel
Right.

Dr. Joseph M. Raffaele, M.D.
But at age 20 something, let's say age 30, they're only losing half that, 0.053. And even at the way over here, you lose... Sorry, let me come over here to this age. Your slope is different there. So slope is 0.03 less than 0.05. So it does change over time, but you have a pretty good idea about what expected loss for that time. So if you're have a 60-year-old, you're gonna say, well, let's say whatever this is right here at 62, you're expecting 0.035, whereas at 25 you're expecting closer to 0.05, 0.06.

Dr. Sanjeev Goel
The one that begs the question that do you think that these telomerase actors might be more effective when you're younger, when the loss is happening?

Dr. Joseph M. Raffaele, M.D.
I don't know if they're necessarily more effective. I think that they are... That begs the question of when do you start taking a telomerase activator? The initial company position is sort of page 40 of about theoretically you could start at 25 to maintain your telomere length. I'm not doing that yet unless I have a 25-year-old who has a telomere length of a 50-year-old, which you do see. But I think you wanna keep your telomere length pretty much the same as it is around age 25 or potentially even younger if you can. That's the way I look at it. There's another reason for that, because of the whole concept of telomere position effect, telomeres are not just about allowing cells to divide, besides their role in mitochondrial biogenesis. And having healthy telomeres allows you to have more mitochondrial biogenesis and healthier mitochondria. Telomerase also regulate the genome by suppressing expression of sub telomeric genes that's called sort of near sub telomere epigenetics, but they also have telomeres over a long distance gene regulation up to 10 mega base pairs away, because of the way in which the telomeres fold around on themselves. And when they get a little shorter, just between let's say 25 and 35, there's a change in gene expression. That may be some of the gene expression changes we're picking up with a test like TruAge, the two diagnostics tests. And so if you keep it the same length and potentially don't get that gene expression change. So these are all open questions still, of course, but if you look at it logically, I think not having any telomere length loss is the best, it's the best thing to do.

Dr. Sanjeev Goel
What is your the longest that you've been tracking TA-65 using patient? And have you seen linked to any of their telomeres?

Dr. Joseph M. Raffaele, M.D.
I have seen length of telomeres in a patient, and the ones I've tracked them is in original patients in the original cohort. And that's 14 years now.

Dr. Sanjeev Goel
Wow.

Dr. Joseph M. Raffaele, M.D.
And myself, 14 years. And I haven't lost telomere length in 14 years. Now, have I gotten older? Yes. See pictures of me when I'm younger, I'm definitely older. So there's other aspects of the aging process, but I feel like TA-65 is certainly done that I have many patients that have had no loss of telomere length and I have had patients who've had significant increase in telomere length up to a kilobase over five years. And then lots of patients pulled out of the immune risk phenotype because of TA-65. I'm losing my lights now. So it's sorta like when the theater dims, the lights come on in the theater and they say that the movie is over.

Dr. Sanjeev Goel
Okay.

Dr. Joseph M. Raffaele, M.D.
And we've been talking for quite a while now.

Dr. Sanjeev Goel
Thank you.

Dr. Joseph M. Raffaele, M.D.
So you have any final closing thoughts?

Dr. Sanjeev Goel
No, no.

Dr. Joseph M. Raffaele, M.D.
Or any questions we can pick up later?

Dr. Sanjeev Goel
It's usually enjoyment. I hope the viewers got something from this, and I've taken back that to go and go get my had telomere testing again, back to for my patients. So I'm gonna start doing that and I'll report back to you at the next summit or some other time we meet.

Dr. Joseph M. Raffaele, M.D.
Yeah, that would be fantastic. Let me just stop the share so I can see it full, there you go. And yeah, so I encourage you to do that. And it's great to have other practices that have the same view of what we should be doing in medicine. And I look forward to seeing you again at one of

the meetings, or maybe popping up to. Why don't you tell the viewers exactly what your social media and your other stuff are so they can know what it is?

Dr. Sanjeev Goel
Yeah, again, my website is longevity.peakhuman.ca. If they wanna email me, they can reach out to my email, which is drgoel@peakhuman.ca. So D-R-G-O-E-L@peakhuman.ca. And I think I'm on Insta. Just look up my name and you'll find me there.

Dr. Joseph M. Raffaele, M.D.
Very good.

Dr. Sanjeev Goel
All right.

Dr. Joseph M. Raffaele, M.D.
Well, thank you very much, Sanjeev. It's been a pleasure.

Dr. Sanjeev Goel
All right.

Dr. Joseph M. Raffaele, M.D.
And we'll talk soon.