Labs in Precision Medicine: An N-of-1 Framework Transcript

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Introduction and guest background

Everybody, Dr. Rob Silverman here, Proof and Health Alternatives. I've got a great guest on today, longtime friend, colleague, and elite natural path and acupuncturist, Doctor Ralph Esposito.

He is Chief Science Officer of AG1. I have to say in a personal light, I remember him when he was just a student in college, and I am so excited to have him on and to see his growth and what he's going to deliver for you in the next hour.

Dr. Esposito, how are things going? Thanks for having me. I'm excited for this. Who would have thought 20, 15 years ago I'd be teaching you a few things.

You've been teaching me a lot in last 15 year that I've already had in hand to get going. So blood labs, They're under fire, they're really actually underwater because people don't take appropriate blood labs.

They are looking at nutritional functional labs and you and I both believe they are over interpreted due to a combination of different factors. So let's set the table.

What factors are these? The number one factor that is not well understood and I think disregarded in many ways is context and history. One of my mentors in school always taught us don't over-interpret labs because the lab test itself never actually treated a patient or cured a Right.

There's obvious exceptions to that, right? You can find a biomarker that tells you that somebody has a terminal disease and you could not potentially save them, there's those instances, troponin for example, yes, that would save a life, but the only thing.

But if we actually take a look at where labs are today and how we look them of all of the AI integrated markers that you can get over a website. What's missing mostly is actually an integration with a person who understands risk assessment and then understands patient history or family histories.

So you really can't get that from not even like a genetic test. That's the major factor that I think is missing is just the integration What we aren't actually paying attention to is modeling and how each one of us has our own individual model that we can learn from.

And I can elaborate that on that in a bit, but what works for you and what is relevant for, you may be very different for what's relevant to the next person and the person after.

So there's a differentiation. So let's talk about the idea and the difference in the overinterpretation of nutritional and functional labs and idea of optimal reference ranges.

Why lab interpretation needs context

Here we have a reference range. Hey, Dr. Rob, hey, Doc Esposito. I got a 31 on vitamin D. Between 30 and 100, I'm good. That's the classic example. Why don't you run with the baton from there?

Yeah. And it also depends on what data you're looking at. So when you look at these data, I think it's good to actually step back. How are these numbers actually determined?

Most of the time, what you are doing is getting very large populations of people running this test so that you get a broad view of their range of markers from the fifth to the 95th percentile.

Now you know what your low and what is your high is. You're not deviating or having it tailored to the individual's personal needs or their family history or anything along those lines.

And that's actually good, right? Because what it's doing is able to catch the ut-oh or the big problems. If somebody is very, very low or very high on a marker, then the probability of them being in trouble or having an issue is very likely.

What we call that is essentially pre-test probability. Before you go into the test, you want to know, before you have the tests drawn, what is the probably of this marker coming back and what does that mean for me?

So prime example of that would be COVID testing. Historically, when we looked at COVID, everybody does a COVID test. whether you're symptomatic or not.

And if you test positive, they treat you as if your positive. But what actually makes that test much more accurate, even today, is knowing what is the probability of me having COVID going into getting that tests done.

For example, symptoms, sore throat, runny nose, headache, that increases your confidence in the result or the outcome. When you start blanket testing for everything, you're gonna get a lot of false positives and false negatives.

So what about there's been some talk about the lack of scientific validation of some of the tests that they're using? And we're talking standardized blood tests.

We're not talking venturing into the functional medicine space, not you and I love the function medicine, but some other tests may be new. Whereas these ELISA tests, which are the gold standard, we know there's not as much scientific data to back up the utilization.

Which tests come to the forefront on tested? You would say, if I came in, hey, Dr. Esposito, run some blood tests you feel most comfortable with. The test that I would feel most comfortable with running or let me start off this way.

Here's kind of the bucket of tests that would want somebody to have as a baseline. I think it might be easier for me to say which ones we should be a little bit more dubious of or questions mostly because those are the things that you should have, you know, a conversation with your doctor about.

So here's the baseline. You always want to get a CBC and a CNP. These are things that are checking for liver enzymes and anemia and blood count. Very underestimated biomarkers are those liver enzyme tests.

That's what you would get in a, a CMP because most people don't know that their liver enzymes are elevated. And I'm not talking about if they're in the 60s, 70s or 80s which would be flagged.

But if you look at a lot of the data on liver function tests, ALT and AST, those were developed in like the sixties. Then as we gained more data, that reference range actually increased.

So the original liver function test ranges, or I would say the flag for high would be above 20 to 25. Now, if we look at a lot of lab tests or lab companies, 40 is the cutoff.

Right. What that tells us is that we've moved the bar because it's now become a norm in our population. Those are the things that I pretty much start with.

CBC, CMP, A lipid panel, you always want to get a basic lip panel. I know there's a lot of these, fancy tasks with lipic particle size and different lipids profiles.

LDLC, triglycerides, VLDL and APLB, they're covering about 90% of what you need there. Then we'll talk about inflammatory markers, comocysteine, HSCRP, uric acid.

Those are baseline fundamental tests. And then we go into the sex hormones, testosterone, estrogen, FSH, LH, depending on if you're male or female.

Baseline bloodwork and key markers

TSH free T4, free, T3. I can rattle them off, but those are the things that I would start at. Here's where I get to the point of the thing that you don't want.

where I see a lot of errors come along are the estrogen testing. So extra dial testing and testosterone testing that is using amino acids. They're not very sensitive.

In other words, they can overestimate or underestimate your actual levels when it comes to estrogen or testosterone. So you want to look for tests that use gas chromatography or liquid chromitography, which are much more accurate and can be more confident in the outcomes.

So a couple of points. There's a lot to unpack, as they say. Number one, you mentioned a lipid panel with an A pole B. To me, that's already getting into part of what's, obviously, it should be rudimentary, but it's getting comprehensive.

5% of the American population has an APOB test. APoB encapsulates all the LDLs, the VLDL, and Lp little a, so I noticed you didn't mention that genetic marker.

So already, That's a big deal. I guess it begs the question, how do you feel about particle size? Before I get to the topic of conversation of testosterone.

You're right, I didn't mention LP little A and that is on the list of things that you want to test at least once. I don't see any necessity or reason to repeat test on an LP Little A unless you're trying to see if an intervention that your doing does reduce LP a little light.

There's some nuances to that. And typically if LP is high, then the risk is elevated for cardiovascular disease, more specifically around calcification on your aortic valve.

So LB little a is certainly in part of that. The LDL particles or LDLP or even the particle size, if you asked me five years ago, I would have said, yes, absolutely want that, want to understand where that is.

If you ask me two years, ago I said no, don't want because all that really matters is APOB and that's actually what's most important when you try to assess cardiovascular disease risk.

Like one of my mentors has told me, you always reserve the right to change your mind as new data comes out. And so I'm not actually saying LDL particle size is a necessity, but there is particular test that I've grown to become more fond of.

I think it's actually a very useful marker in this age of stat and use metformin and GOP1s, and that's LPIR. So LPIR is a type of test that can use lipid particles or LDL particles to understand your insulin resistance risk.

Well, most people don't understand is that yes, insulin is a great biomarker for GLP one for, excuse me. Insulin is great. Biomarkers for insulin resistance.

But in a world where we're taking medications and supplements that actually can artificially change insulin, like base, some agglutide or to Zepatide, which will artificically increase it temporarily and then eventually lower it.

And you won't see much change. And LPIR can help you identify if somebody is still at risk for insulin resistance. And so that is a way that I would use it, but I wouldn't use for cardiovascular disease risk assessment.

Yeah, I'm big on LP little a, and I do agree with you on the need to do it once, because you want to set a standard,

not necessarily for the individual.

It's the heart attack genetic marker, But you can share it with their family members. Only about 1% of the American population has had that test. That's horrific.

Statins raise that marker, and I'm not anti-statin, just that's what the data dictates. Niacin treatment is shown to lower Lp little a by 23%. Post-menopausal women have an increase in L p little A.

And something that I am sure we will table for now and get to testing APOE, absolutely just rocket ships L P little. But what I really want to get too is the testosterone conversation.

Everybody that's my age, I'm 60. Every one of my guys, if they're not on TRT, want to be on Trt. And none of them asked the question of what like you said about gas, liquid, amino acid.

As a matter of fact, aren't there several different scales of testosterone? So if I say I have 550, That's going to mean something vastly different to you than to me and then possibly the guy in the corner.

That is absolutely right. And so the endocrine society will essentially say they set a lower limit. and that's really where a lot of the data is most convincing or most strong.

We don't know if somebody's testosterone of 500 is better than a testosterone 900. There's actually no data to suggest that if you are at 400 or 500 total testosterone and we bring you to 900, that you have better health outcomes or better muscle mass building.

We think that's the case. And usually that is the through exogenous testosterone injections. Where the data is strongest is when you take somebody who is low, and depending on the society or the institution, it's around 250 nanograms per deciliter.

When you get somebody with below 250 or around to 250 and bring them to what we will call a normal physiologic level, these are using ELISA assays. So I would say the less accurate way to measure it.

That's where the data is strongest to suggest that you actually have benefit and you improve things like sexual function and muscle mass and even cognitive functions.

Lipoproteins, insulin resistance, and testosterone testing

But we don't know if getting somebody from 400 to 1,000, whether it's exogenous or endogenous, actually has a benefit. I would imagine it helps a bit, but we can't measure that.

When you say benefit, you're talking health benefit or looking more jacked, if you will, as they use in vernacular. I would say a health benefit, we don't know.

We know there's health benefits from going low to normal, but we do not know if there is a healthy benefit from normal to high. And the reason why that is, is there are these things called CAG repeats, which are essentially the way our DNA is sequenced.

And depending on the ways that those DNA molecules are built, it will determine how sensitive you are to testosterone. And so you may respond more sensitively to a 400 than I would.

And I might need more than you would, but we can't measure that yet. In other words, we want to make sure that it's tailored to the person. But if you had to do like a big broad view, it is really low to normal where the most bang for your buck comes from.

Let's do a little New York City rapid fire. I got a NewYorkCity slash Westchester guy here, so he'll be able to motor. Number one, TRT, side effects. Elevated hematocrit and hemoglobin levels is really the biggest concern because

that actually results in actual health risks such as increased risk for cardiovascular disease, stroke, blood pressure.

That's the big one that I see most cited in the literature. Other side effects, if inappropriately used, such as kind of comastia so increasing breast tissue and men.

It can actually cause acne in some men, but again that's really if you're abusing it. elevated PSA levels. So there's not a prostate problem per se, but PSa levels, which is a process specific biomarker that can elevate, that could cause concern for men if they don't have any history on their prior PSL levels or your prostate health.

What I've heard from the male hormone experts is that it may raise PSA, but it doesn't increase the incidence of prostate cancer. That's right. Hair loss, yay or nay?

Yes, I forgot that. I forget that side effect. Yes. It just took me out. Let's say I'm done. Not in everybody, about 30% of men may experience it. And that can vary depending on the population.

So what's the white marker to test for somebody's testosterone level? Is it total? is it free? I know you don't like estradiol. Everybody wants to know what the right markers, what should they be looking for?

Yeah, this is not going to be a popular stance. Sorry about that. That's okay. Again, if you asked me five years ago, I probably would have said free testosterone and total testosterone.

Then the question becomes which free testosterone direct or calculated? all of the data or majority of data is uncalculated. So you have this specific algorithm that'll measure your total testosterone, your albumin and then sex hormone binding globulin.

And then you do a fancy calculation that I don't know and you would get to your free testosterone levels. Now we have advanced technology that can measure how much testosterone in your blood is unbalanced or free.

very little or relatively little data on free testosterone direct compared to calculated. In the end, a vast majority of the literature on testosterone is on total testosterone.

So, I am in the camp of total to start on first and then free to stop shown if the total is awesome actually doesn't tell the whole picture and things don't align with the symptoms.

What's the proper ratio or the optimum ratio between total and free? You want free testosterone to be anywhere from one to 1.5% of total testosterone.

That's about how much it exists in the blood. You can get up to 2%, but typically once you start trending below, once they're getting closer to the 1% a free to testosterone, to total, testosterone I start getting a little bit concerned that there's other things in there that are binding your testosterone What's a good number?

Cause I hear all these different numbers. Hey, Dr. Rob. I mean, I have guys that come in and they're just stacked. They're muscular and there at like two 60 and their in their fifties.

And I'm like, dude, you need any testosterone. You're put together like a bear. Other guys who are kind of thin and don't look like they can do a pushup and I had like nine 50, a thousand and then not using any replacement.

Help me with the numbers and help explain to me how you have those two physical scenarios. The data would say if you look at the number 250 is low and 900 is pretty much about 95th percentile.

So if we have a testosterone of 900. you're pretty much higher than 90% of men in the population for what that lab has tested. Again, these are all lab-specific numbers.

Then you look at other endocrine society and neurological associations, you'll see other data. I like to see men ideally above 500 nanograms per deciliter.

It doesn't sound aggressive. it doesn' sound crazy to say that's achievable, whether it's endogenous or you make it yourself through lifestyle interventions or exogenous.

That's where my cutoff is. Once you start trending below 400 to the 300, I start then pairing that with symptoms. Many associations would suggest that you shouldn't treat a man or even test a men for low testosterone if they're asymptomatic.

I don't entirely agree with that because there's actually other benefits of testosterone, like cardiovascular disease prevention, insulin resistance, protection, bone density.

And although we don t have data yet on it, it could be protective for brain health. Um, and the data on brain now is really of the opposite is when you deprive men of Testosterone, what happens to their risk for dementia significantly increases.

So I would say those are the four characteristics that I'd say, if these are problems, you want to make sure that somebody's testosterone levels are optimized.

So you are not anti-TRT. And we're going to segue to another section. It's nuanced. You're not trying to be dogmatic about it. Something I wanted to ask you, I've heard these terms, population reference ranges versus individual clinical prevalence or decision-making process.

They're two vastly different things. Again, it's getting back to that reference range in the right column. Yeah, and that's where individualized and precision medicine is going, where it should be.

We don't have enough data or technology to be able to know exactly what is right for you. I'm sure if I plug this into an advanced AI model, of course, that it would be able to give you some type of assumption as to what a risk level for your vitamin D or your B12 or home assisting should be.

What is missing from that is symptoms. And so these are, I would say, signs and symptoms, so symptoms are what I tell you signs are.

TRT risks, thresholds, and symptom-based decisions

What I see. So if I. See things that are throwing me off. low energy, apathy, low libido, load drive, no confidence, difficulty making decisions. These are all things that could be signs of low testosterone.

They're not pathognomonic. In other words, if I said those things and you said, oh, that's me, it doesn't necessarily mean they have low testosterone levels.

So you have to combine that along with the biomarker to put them together and say, is this actually working for that person? When we look at the reference ranges, again, what most people don't understand is that these reference range are from the fifth to the 95th percentile.

So you literally have to be in the lowest fifth percent of the population or the top fifth of a population to to flagged. And it matters on what you're actually testing.

If it's testosterone, then, hey, like I don' want to see, I really want A or A plus. Same thing with lipid and lipids markers. For example, triglyceride, I actually forget what the actual cutoff is.

I believe it's 150 milligrams per deciliter. And the reason why I say I forget that is because my cut off is 100. So like that as cemented, printed in my brain.

but most doctors won't flag anything until you're 151. That is way too high for me. Cardiovascular disease risk and stroke risks and insulin resistance significantly jumps once you get to that level.

I don't wanna wait for that levels. So again, it has to be nuanced based to the lab, but I would say things like CDC panels, like hematocrit hemoglobin, red blood cell counts, you know, CMP, where you look at things, liver and kidney function, those are things where the reference ranges are appropriate.

When you get to more of the markers that impact the function or chronic disease prevention, that's when I get a little bit more picky about my targets.

So to recap, population reference ranges show what's typical for what they deem a healthy group. That's 90 to 95 percent of people acting as a general healthy benchmark.

Good luck. Individual reference ranges or decision limits or specific thresholds used by practitioners to make decisions on one patient. Which is going to get to where we're going talk about your N is one or N equals one, which I love.

You mentioned lipids and heart attacks and everything like that. So let's segue into that, the number one killer. cardiovascular disease. Most Americans don't know that and they don t seem to respond when you say that.

Interesting, we're talking about labs. 50% of heart attacks, people have a normal lab. The number one benchmark, which isn't a blood marker, is blood pressure.

How am I supposed to go about explaining all that I just gave you to the general population and patients in general? I thought you were going to go somewhere else with that, which I think is important to mention.

One of the first symptoms of a major adverse cardiovascular event in a male is a heart attack, right? So I told you we're going there. That's a big one.

So think about it. You don't know if you're at risk for about 50% of men. If you are at-risk until you actually have the thing that is at huge risk factors, blood pressure, incredibly underestimated.

Now, If I had to say, what's more important, measuring your lipid biomarkers every three months or getting your blood pressure measured once a week until you know that it's stable, I actually would go with the blood-pressure because it is a modifiable risk factor.

So here's a nuance. People think that here are risk factors. And if I modify the risk factor, if improve that risk, factor the risks for the disease goes down.

That is not true. So there's modifiable risk. Factors and risk factors. For example, blood pressure is a modifiable risk actor. Good point. If your blood, pressure's high, And that's a risk factor.

That's saying, yep, my risk for stroke, heart disease, diabetes, cancer, et cetera, all these things go up. And if you lower it, your risk, for those things actually go down.

There's other risk factors that we can measure. Like, I don't know, you're a poly genotype. can measure that, but it's not modifiable. I can't change that.

And even if I were able to change it, that doesn't necessarily mean that my risk factor for Alzheimer's goes down because it a pleiotropic disease. In other words, it not just your gene, there's multiple things that are involved.

Right. Exactly. So when we look at risk factors, It's very important to think Is this a market to tell me if I am at risk? That is great, because then you know what to do to reduce the risk of the disease to not necessarily fix the number.

And that's where I have a little bit of a battle to pick with some of these medications that like GLP-1s and terzepatide and somaglutide is you're reducing the risk of, you know, of these diseases from the weight loss.

Right. And then when you regain the way, do those things come back? They do. You do regain. The way your

blood pressure does go back up, your weight and your liver adiposity does.

Go back. So that's where I think it's a really important thing to understand that reducing. Weight loss is great. If you can sustain the other things that come along with it.

Otherwise, those risk factors come back, and then the disease risk also resumes. To speak to the GLP-1, so what you're saying is you being very kind, that you believe that the doctors who prescribe it should also be prescribing a lifestyle change with it.

Of course, I'll sidecar and say I think maybe in many instances, not all, They should look to natural approaches and lifestyle changes. You know, the GLP-1 is exemplary of the gut-to-brain axis.

There's the glp-one receptor side on your intestinal tract, on you lytic cells, there's one on the vagus nerve, which carries it to the dorsal hypothalamus in your brain.

Well, that sounded really good, but what does that mean? It means when you stimulate and communicate between your gut and your brains, you'll have a sense of fullness satiety.

So I concur wholeheartedly with you and also I guess we should say 40% of the loss of weight comes from muscle mass, but you also lose heart muscle and particle size.

I'm not that smart. Maybe you are or maybe we need to find somebody to tell us how to get that muscle mess back in our heart. And lastly, we talk about high cholesterol and statins are used.

I think they're the most prescribed drug in America today. 92 billion Americans have or utilize statin. Statins decrease GLP-1 over a four-month period by 50%. So here you have somebody who's a little heavy, who has high-cholesterol, was on a staten and his GLp- 1 goes down.

And yet the statin may have caused the need for the GLP-1. I'm perplexed. Help me, please. Or very complex issues requires a very comprehensive approach.

And so I don't think I would do anybody's service by saying it is this intervention, this is the explanation for why those things happen.

Population ranges versus individualized medicine

There's so many nuances when it comes to human physiology. And in fact, if we think we know everything about the way that the human body works, then I think, we all need to be humbled a little bit by what we actually learned over the past 30 to 40 years when It comes just to the microbiome, right?

We thought that everything was sterile. And that's actually not the case. Yeah, without question. I know you have a child and I'm sure that he plays with his hands in the dirt and you a dog already and things of that nature.

A little again, True Fall said, let you expand upon it. So I wrote down here, traditional labs are designed to detect disease, not dysfunction. You can feel terrible and still fall within a statistical normal.

Functional medicine. looks for patterns of optimal markers, early inflammatory shifts, mitochondrial strain, gut to immune imbalance. That is true. So would it be fair to call it root cause or root causes resolution?

Partially, I would say. And the only reason I say that is because I do think sometimes the diagnosis matters. There's this, there's suggestion in a lot of the functional medicine circles that it doesn't matter what you call it or what the diagnosis is where it really you're looking at whether it's a function or a dysfunction.

But by definition, understanding what pathology is helps you understand that pattern so that you can intervene better. So yes, it is appropriate for unique situations where the whole picture doesn t make sense, but I do think

that understanding the typical pathophysiology of a disease by definition is incredibly useful and powerful.

And we should use it to our advantage, but not let it limit if anything falls out of that category that we can actually intervene. How can we use serum testing, blood testing if you will, to see what's happening years before a diagnosis occurs because we know that we're looking at after the fact in many blood tests.

How could we portend the diagnosis? It's very simple. Look at the data that helps you understand what numbers or what values predate onset of disease.

We don't have that for a lot of diseases. Insulin is a great one. We actually do have the data that an insulin level or elevated fasting insulin will predate diabetes by anywhere from five to 10 years.

The same thing for an oral glucose tolerance test that will pre-date an elevated A1C five, to ten years, so let's use that. Do we know what a LH or FSH elevation or a low L or FSH level means for somebody's risk factors for having low testosterone in 10 years?

We don't because that's a very complex condition. So we often dismiss or don t even look at the data on the insulin or fasting blood glucose or glucose tolerance test when we actually have it.

And so the answer I would say is look directly into the literature, not necessarily just the guidelines. How do you feel about advanced tools like methylation testing, stool testing genomic testing?

for the right purpose and if you have the retest probability. So essentially, once you had this model of how things could work and that test provides more data to allow you to advance your models that you can actually target as a person, I'm a big fan.

I do use GI testing or gut testing for microbiome testing, whether it's PCR or whole genome shotgun sequencing. or inflammatory markers like CalProtectin and secretory IgA, those are all very, very helpful and I find them very useful.

There's a handful of genetic tests that I think are very healthful MTHFR, MTRR, APOE genotype, multiple others. Do I thing getting a whole genome sequence is really going to change the way that i treat the person?

I don't think so. unless we're in unique situations where we have very rare conditions and we don't know what's going on. Interesting. So you specialize in the idea of individualize and personalize a treatment protocol for that person, taking all the dots on the data, if you will, putting it together and giving the person their best outcome.

They call that N equals one framework. How'd you come about this? And what does that really mean to you and everybody listening? The N equals one or the N of one framework is essentially a way to develop a model that allows you to apply all of this vast majority of data that we don't realize, but we're pretty much flooded with every single day.

on social media, eat carnivore, don't eat a carniver, go vegan, test your blood type, Go get this other biomarker.

Cardiovascular risk, blood pressure, and GLP-1 nuance

Don't drink that in the water because of the class. Literally there's an immense amount of information that we're being flooded with, but very little data.

And so the way that I look at it is it's actually fascinating and mind blowing if you think about it this way. When you look at an individual patient, let's say you're my patient and I have you in person, what I'm going to do is I am going look you, following the conventional model, I would say, Hey, Rob, I see you're here and you have this blood test.

If I look at the data on 20,000 people and let's say your LDLC is 90, not high, no low, just kind of average. Not average, but nothing to be super alarmed about.

I would say based on the date that I have on 23, 30, 40, 000 people, you fit within what's acceptable. But the contrary of that or the converse of, that would be here, I have 20,000 data markers.

How does that apply to you is where really N of one works. So I take data from 10,00 people, 20 thousand people and apply them to, you rather than taking your numbers and applying them, to an immense data set where you kind of get lost in the noise.

It's more of a bottoms up approach where, and then say, how do you fit within everything that I know? Rather than saying, here's where you've fit in this universe of data.

You're fine. Nothing to worry about when in fact you're coming to me and saying I'm not fine, there's something wrong. Fascinating. So I believe that if we were to talk about the next five or 10 years where medicine is going and functional medicine, obviously AI has grown leaps and bounds every week, every day.

I think this concept of precision medicine is right there with it. Health detectables, which I should ask you, how do you feel about them? Would you recommend them for patients?

Which ones if you want to venture into that to get or help you with your N equals one? Yeah. So I'm half cyborg by many, many times of the year. Clearly.

I've, I At points in the year, I've had a whoop at Apple watch and or ring a CGM, a ketone meter, like I'd done all of them. The one that is helpful the most is the one you could be consistent with.

And that's really what works best so that we can understand deviations and trends, not necessarily absolute numbers. For example, my HRV, Great marker, by the way.

Great market. But it's not a modifiable risk factor. It's a risk actor that you can identify. That was a great point. And if you could reiterate that again, just in case somebody came in on a podcast, risk-factor-first, modifiable risk factors.

I think that's, you know, a gold-mating-win statement. Sure. So a Risk Factor is essentially something that to help you identify whether you're at risk for a disease or not.

So you might say, hey, I have a elevated blood pressure. That is your risk factor. But that is also a modifiable risk vector because you can change it and actually reduces the risk of a.

Disease.. So a modifyable risk factors, something where it's something that tells you that a problem is going on or you are at. Risk of. A problem happening.

And you. Can do something about that metric. a risk factor really just tells you whether you're at risk or something. But if you change that number, it really doesn't change much about whether that disease is going to happen or not.

It's just a clue that something is off. An example of that would be HRV. We know that when HR is really, really low, and again, depends on who you ask what low is, I would say anything below 30 to 20, right?

That is telling you, hey, there's something going on here. There's nothing wrong with my nervous system. But just because you have a higher HRV doesn't necessarily mean, or if you get your HRB higher, doesn' necessarily means that you solve the problem.

And where I was going with that is seven years ago, my HRRV on average was about a hundred. It was crazy, right? Yeah. I mean, that's when I first started getting involved in into the aura ring.

And I spoke to somebody at aura, and they were like, we don't see a lot of it. This is when aura was not huge, right? So I'm sure they see A lot more of that.

But their response was, That's kind of unicorn ish. We don' see. A Lot of my HRV now around 70. Still high. Yeah.

So if I told the average person, Hey, my HRV is seven.

They're like, Whoa, what did you do to get that? My response is, is I'm unhappy with that because I know it was at a hundred when I felt my best. When I was feeling well.

And how do I modify that and go in the sauna? and I do a 20 minutes sauna and my HRV the next morning, high 90s, maybe a hundred, right? That is telling me that I understand how to modify the HRT, but doesn't necessarily mean I'm changing the course of disease or progression on that metric.

So the change is really most important. Great point. And bringing up sauna is exciting because I sauna, you know, five days a week, three to five at minimum.

And modifiable risk factor is being modified by a lifestyle hack. So I think you just pieced it together and you did the locking key version. And yes, we are both very robust on the data for sauna.

Let's share some quick hits. 175 degrees approximately. You want your head out of the sauna The whole idea is to have a little hormesis, a strain to the body to release heat shock proteins.

Functional medicine, early detection, and N of 1 care

Then if you really have courage, you can go in a cool dip, not cold dip but cool at about 50 to 52 degrees. If you want to be like Mark Wahlberg and go on an ice and freeze your fortitude, God bless.

Yeah, I see you shaking your head, no. Not a good choice for men and women. Particularly for women who are under the daily stressors of hormonal fluctuations or muscle recovery, etc.

I'm not very bullish on cold plunges. Mm hmm. It's great for athletes who need to feel less sore or recover immediately, but actually the long term data on cold plunges and we're talking, you know, ice cold plunge is actually not beneficial for muscle recovery.

I agree with you because I think the biggest problem with the women you were referring to, which is perimetapausal MT, metaposal transition is that any kind of stressor to the body fluctuates the hormones even more.

And that is their number one problem. Their hormones are fluctuating. So, I mean, it's like this big precipitous wave going up and down. I agree with you there.

But sauna, everybody, if you get a chance, go for it. Love it, it's one of the, you don't really have to do much. You just have sit there and suffer a little bit, but it is incredibly helpful for cognitive health, for cardiovascular health.

And in fact, these are things that traditional medicine has been doing way before the biohackers got hold of it Right, biohackers are an interesting group of guys and gals because there's a lot to what they say, but sometimes they become very zealot in that it's correct.

And what you're saying is, as the data comes in, I may have to change my position or my positions may evolve as I learn more because it may say one thing in the literature, when I apply it to a patient base, it is different because science has to lead to application And results in a patient population, because if it's a bunch of mice, that's all well and good, but that doesn't necessarily mean it is going to work or not work for me, which comes to the next question.

Which nutritional biomarkers are commonly misunderstood or over relied on? I would say vitamin B12 serum levels is very misunderstood. I see a lot of doctors and actually patients freak out when their vitamin b12 levels are, you know, above the upper limit.

And I really don't see any risk in that I'm not concerned. Does that mean you're taking a lotta b 12? Probably doesn't mean You need that much. Maybe not, but it's not a actual risk factor or concern.

I do actually get concerned on the opposite end of that when your B12 levels are 300, 500, not flagged and not very, very low, but That is actually a risk factor.

And if you look at a lot of the history on how the B12 levels were actually determined, it was based on people with a type of anemia where your body doesn't absorb B 12 and you're using a disease population to apply to a healthy population in the 1950s.

So totally different reference range and different population. Then really the metrics that I use for B-12 assessment would be homocysteine and methylmalonic acid.

Those are functional markers that tells you what the B12 is doing in the body. So that's one that I think is misinterpreted on both ends. The other would be vitamin D3.

I mean, very controversial. Ideally like to see levels above 40 and probably depending on the time of year in a 60 to 70 range, whether you're cold weather, flu season, et cetera.

Do I think there's a benefit of having a D3 of a 250 HD3 at 90 or 100? Probably not, but there is actually very little risk on having it there. But again, I'm really at the minimal effective dose rather than just trying to get somebody to take, you know, get a high score.

So I am going to go a little out of your comfort zone. I will take AG off the list because I just don't want to put you on the spot on that. Give me five supplements that you would recommend for people who have good overall health.

and enhanced optimized longevity? Baseline would be omega-3 fatty acids, specifically EPA and THA. Very, very bullish on those. I don't have much concern about the potential side effects that people say with arrhythmia.

If you look at a lot of the data, there's a lotta noise there and not really great signal. So EPA, DHA, which are omega three fatty assets are my number one.

My number two is obvious vitamin D3 and K2. Always with vitamin K 2 and vitamin d3, you have to tailor your levels based on what, sorry, tailor dose based some of your level.

Number three would be two forms of magnesium. magnesium glycinate or bisglycine, same thing, and magnesium threonine or magteen. Those are the two forms of magnesium that I've found to be most helpful, not just for getting your magnesium levels to sufficient, but also to provide magnesium, that can actually enter the brain and function for brain health.

My fourth would be Theracumen specifically, no affiliation with the brand. I'm a very big fan of a specific form of curcumin called Thercumin, which actually has been shown to potentially reduce amyloid plaque in the brain in human subjects.

So not many other types of Curcumen have done that. Very bullish on that and I take it myself.

Wearables, HRV, sauna, and cold plunge debate

And the last, it's kind of hard push between lutein, zeaxanthin or cocoflavinols. The data on both of them are so strong. It just really depends on what your goal is.

I tend to go on the copoflavinol side, mostly because I have a family history of dementia and Alzheimer's disease or Lewy body dementia. And so I try to protect that, but then the data on lutein and zeaxanthine, which are carotenoids is also blooming.

So you're asking me to pick between two things I love, it would be the cocopoflinol. You can have one on deck, It's okay. Okay. as anti-inflammatory. Let me throw out some other supplements that are deemed anti inflammatory and I'm going to let you rate them, discuss them.

However you feel. My favorite, and don't let that push you in any one direction, are pro-resolving mediators, the fractionated breakdown of fish oil, which doesn't happen in 97% of the population.

How do you about PRMs, if you will? I like the idea of PRMs. I don't like scarcity of data on PRM specifically around health outcomes. There's tons of protozoan mediators.

that are coming from DHA and EPA. Most supplements are isolating them, depending on the brand, between like three to five of them. I actually really do like them I like the data.

Um, I liked the physiology of it. And I actually take a high amount of EPA and DHA. So I think I'm getting most of the benefit. I like it, but not enough to actually have it become part of my stack.

Okay. The way I take it is I just take them with the omega-3 fatty acids. Difference, all acceptable, agreeable difference. How about PEA, the eukarbonite system?

I have not seen many patients benefit from it. I've tried in several patients who have had multiple different things. They've combined it with CBD and other anti-inflammatories.

But I haven't seen it move the needle on people. Sounds interesting, very plausible, maybe not for the right patients that I tried to use it for. So it's interesting and I like it, but it doesn't fit within my paradigm.

How about the new nutrient that everybody's talking about, i.e. a spice called saffron, which I call the turmeric of 2026. How do you feel about that?

I love saaffron actually, especially for mood. But surprisingly, there's a very good amount of data on saeffron and sleep and more specifically, feeling refreshed in the morning.

And that's really what matters, right? So we could all take melatonin, which I am a fan of. I'm not opposed to melotonin. Like I not villainizing melotony here.

But if you want to fall asleep, meletonin does a decent job. Or you could take other things too. Saffron is actually for the morning after. So it's really for ending your night and starting it right.

Or starting the day right, I would say. Safran has a very good data around that. Anywhere from 28 to 30 milligrams is where I always start. I'm a big proponent of saffron.

health-promoting benefits for years. It's good for sleep. Great for the cytokine storm, i.e. anti-inflammatory. Believe it or not, it's a major go-to in an intervertebral disc injury.

Decreases cholesterol, decreases lipopolysaccharide, LPS. But here's the little nuance, using an idea that you do. If you have Parkinson's disease, Don't take melatonin.

One of the biggest problems with Parkinson's is when you look at light, you stare because Parkinson has a decrease in dopamine.

Misunderstood nutrients and supplement stack

and dopamine allows for a coordination but involuntary muscle movement which is your blink reflex and you're looking into the light because you trying to stimulate melatonin which will decrease your dopamine.

So everything's good except for this quickest growing neurological problem called Parkinson's. In those cases, no melotonin, which really begs the question or gets back to the point about that individualization that N equals one that you are leading the charge on.

Yeah, I would also, that's a fascinating fact there. And I think it's important for people to take that home. On the

other side of it, there's actually positive, possibly beneficial data for being protective against Lewy body dementia, which is why I take it because my father had Lew body Dementia.

They're just different in Parkinson's per se. Which is very different. Yes, right. So again, two neurodegenerative diseases. And this is where I think the battle of functional medicine versus conventional medicine is a diagnosis.

Is it the function? It's both because what you just told me is Parkinson's. I know that I can't treat that the same as Lewy body. But I do need a part of functional medicine ideology, systems-based biology.

I mean, really, that's what functional meds is. It's systems based biology in an application. And if you can incorporate that, then you know, okay, in this pathology, the system-base biology works in one way, but in another pathologist, it works on a different.

you do want to work on the function of how those things are working, but you need to be guided by what we know on how that pathophysiology works. So that's a great example of something we discussed earlier.

To piggyback on that just a little bit, the difference between Alzheimer's and Parkinson's is there are different genetics. Alzheimer is much more genetic-based than Parkinson.

I think it's 10 to 15%. Women more commonly get Alzheimer. Men more commonly get Parkinson's. Parkinson and Alzheimer's are both gut originated, their gut to brain axis, the bidirectional, they're both autoimmune.

And this would be a, you know what, we'll bring it back. Let's go for it. and let's have part two on the seminar podcast, a whole bit. let us do the whole kid in Kabuto.

That said, I always like to end with a question for a buddy of mine. He's my biggest supporter. he listens all the time. In Switzerland, everybody's heard about him.

And he says, Rob, i need one thing to change my life for Monday. I just want one. Dr. Esposito, you're speaking to my buddy. What's that one things he needs to do differently?

on Monday morning, he should have a gratitude journal and just write one thing that he's grateful for. I think in this whole fancy schmancy approach of what blood tests to get and what specific supplements to take and What should your zone to be or your HRV?

What we overlook is community and gratitude, which has a significant impact on how we feel, but also on health outcomes. So I would say write one thing that you're grateful for.

There you go. It's been a great hour, Dr. Esposito. We have to do it again. It's exciting and you know what, when I first met you, I knew you'd be here and I expect big things from you in the next decade.

So keep going. Don't stop and stay on your mission because you've got the greatest job in a world. You get to help people. you're making an indelible mark on people's lives.

Keep going! Thanks so much. My pleasure. We'll see you soon everybody.