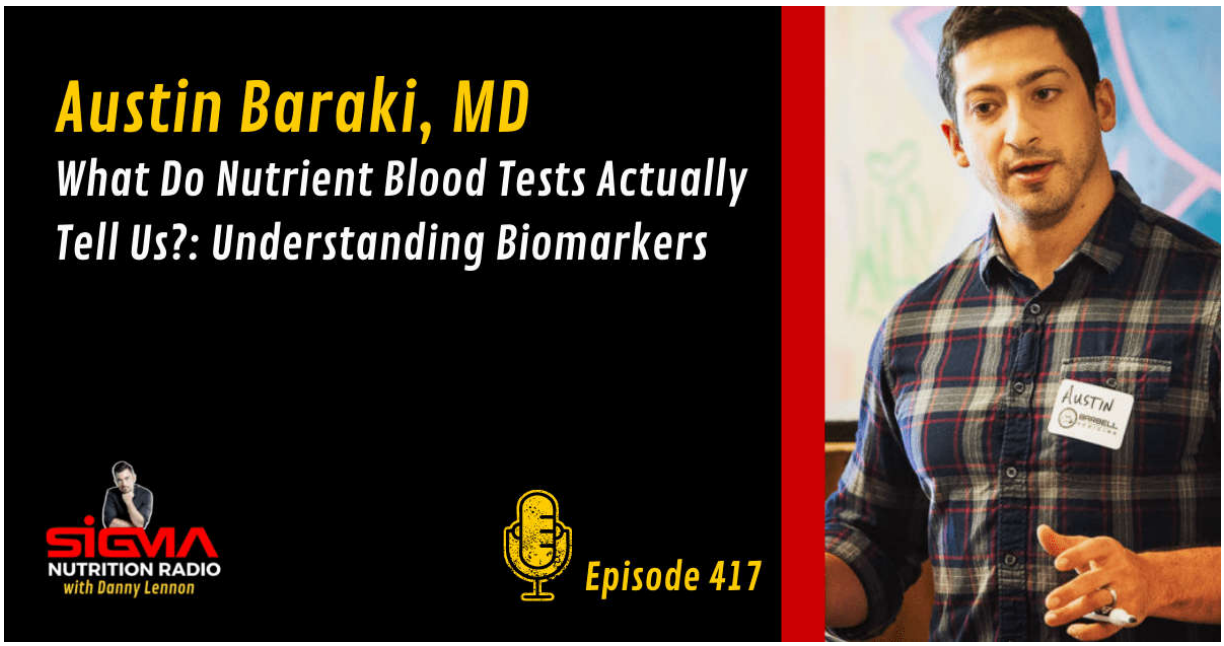

DANNY LENNON: Okay, and here we are. Welcome to another episode of sigma nutrition radio. I am Danny Lennon. I am of course here alongside Alan Flanagan. Hello, Alan, how are you?

ALAN FLANAGAN: I'm good. I'm good. I'm looking forward to some I guess we could call it mythbusting in many ways on on today's topic.

DANNY LENNON: Yeah, I think so we've been joined by a very special guest, a returning guest to the podcast, Dr. Austin Baraki, a medical doctor, strength coach, powerlifter, liver kingfanatic. We can say we're going to follow up actually on some things that we discussed on that previous episode with Dr. Baraki, as well as some areas that we've been touching on in previous episodes of this podcast. Notably, if you've listened to our recent discussions on sodium and health, as well as our bone health episode, there will be things that are relevant to that, but I think we'll expand on and get into a bit more detail. But before we get to that, welcome to the podcast, Dr. Austin Baraki.

AUSTIN BARAKI: Hey, thanks for having me. Glad to be back hanging out with you guys.

DANNY LENNON: We have a lot to get through. But I guess as a nice way into this topic, we have been discussing recently, the topic we're going to get into today. But it kind of came to mind off the back of the bone health discussion that Alan and I had relatively recently. And you were talking to us about a particular point that could have triggered off a series of thoughts I think we're going to expand on here. Can you maybe just elaborate on that for people and kind of what was the thought process in the particular bone you have to pick with a certain idea?

AUSTIN BARAKI: No, I see what you did there. Yeah, so for folks who listened to the previous sigma podcast that I joined, you guys for we talked a lot about, basically biomedical testing, and the different ways that testing can be deployed in practice, whether in the capacity of medical screening, where you're looking to identify conditions in people who have no signs or symptoms of disease in hopes that early intervention can modify their health trajectory. Or the second way would be in the realm of diagnosis, where you're searching for a particular condition in an individual who has, you know, signs or symptoms of a disease or some sort of pathology. And when I was listening to you guys episode on bone health, what came up i your conversation I think it was Danny, you asked a question about the role of measuring a blood calcium level as it pertains to bone health, as it pertains to osteoporosis, or even just like dietary calcium and things like that. And so, you know, we ended up chatting a little bit after that, because it struck me that, you know, that's a very on its surface, on it's on its face, that seems like a very plausible kind of question to ask, like, hey, if you're, if you want to know how your bones are doing, just check your blood calcium level. And if your calcium levels good, then that tells you that you know, you're in good shape from like a nutritional standpoint with respect to your calcium intake, and the amount of calcium in your body and things like that and that kind of brought to mind a lot of things that I see in practice with some folks who are generally, you know, health conscious, motivated, you know, training individuals a lot of times and they want to be proactive about their health, and

they might go out and get labs done, because they want to see where they're at, for example, or they might have a medical condition and get tests done. And then they might get the results before they've had a chance maybe to talk to their doctor or something like that. And they might look at some of these numbers and you know, kind of make assumptions about the meaning of these numbers or what they imply or how to interpret them or what should be done in terms of, hey, my calcium is a little low or a little high, or sodium is a little low or a little high or same with potassium, or any number of vitamin D, any number of other things that we'll probably be tackling here. And it just is readily apparent to me and day to day practice that the interpretation of biomedical testing in general is extremely complex and nuanced and case, it depends a lot on case context and things like that. And that is generally under appreciated by the public, particularly those who go out and get their own labs done, which is happening a lot because I see that they get their labs done, and then they get the results and they are like, oh, I'm not sure how to interpret these let me go message and they messaged me or something or post a question to our forum or our group and ask questions, hey, what does this mean? Which the first question is, okay, why was it measured in the first place, but you've already kind of skipped that step. So to summarize, you know, when you asked about, hey, serum calcium and osteoporosis, and it seemed like a plausible question, but there's like a lot more to that topic in general in terms of how would I even interpret a blood calcium level in somebody as it pertains to their bone health. It's very tricky.

ALAN FLANAGAN: I was going to say it's, you know, because Austin mentioned, you know, it's underappreciated by the public, it's underappreciated clearly by the research community as well, because the context in which that came up was in reference to a particular study that was a Mendelian randomization study of serum calcium levels. And so the conclusion was, oh, well, it's not causally related, we were like, Well, why would it be because serum calcium is likely telling you nothing. And so you're getting really a paper that's just a house of cards so

to speak, that's not really telling you anything in relation to the relationship between calcium as a dietary exposure, or even a supplement and the particular outcomes of interest in that case, we were talking obviously about osteopenia, osteoporosis. So you know, the fact that wasn't even appraised at the outset as a research question at that level is where that should have ended. You know, but clearly, it didn't. And you know, you go ahead and you do a full paper on a, essentially a useless biomarker. So yeah, I think it's really important for the research context that we might consider some of these exposure outcome relationships as well.

DANNY LENNON: Yeah. So and that actually kind of sets us up nicely. Because yeah, that that pondering had of, well, what is the relevance of serum calcium in this context, relates down to thinking about calcium homeostasis, right? So when we're now thinking about, well, what do these different markers mean, where they might be useful, where they can kind of misleading that gets us into, we briefly I think touched on that podcast of the role of things like PDH, and how that impacts serum calcium, then why it might not be a useful idea. I think this is something that's worth kind of fleshing out a bit more. So maybe Austin, can you maybe if we focus on calcium, specifically for the moment, and we were thinking about either serum calcium or other measures that relate there what do we need to know about calcium homeostasis, the different players that are involved in that and therefore, where does that leave us in relation to measures of serum calcium or other measures that may come across in context related to bone health or otherwise?

AUSTIN BARAKI: Yeah, I think going through this as an initial topic lays a lot of themes that would carry over to a lot of the other similar kind of biomarkers that can be measured as well. And so I'll kind of try to point those out along the way. But one of the important considerations when you're checking any kind of biomarker is what tissue compartment are you sampling in the body. And the reason that's important here is because 99% of the calcium in the body is in bone. It's like locked up,

and we're not, you know, biopsy in people's bones or something to measure their calcium levels, instead, we're drawing it out of their blood and if 99% is locked up in bones, then yeah, like 1% or less is actually floating around in the blood, but that's what we're actually measuring. And then even within the blood, there are two different compartments, there is the fluid that is outside of our cells , or the extracellular fluid. And then there is the fluid that is inside our cells, because all of these things do not freely, you know, flow across our cell membranes. And so of the it 1%, that's not in our bone, most of the remaining calcium is actually sitting outside of our cells with a very miniscule amount sitting inside of our cells. And knowing these kinds of different compartments, again, is one of these themes that will carry over and some of the other things that will mention. And so this division, or distribution of calcium across these different compartments is real important. Calcium outside of the skeletal bone role, it plays important roles in muscle contraction, nerve conduction, it plays a role in in blood clotting, as well. And so there's a bunch of other functions besides just very important functions that are critical to life, aside from just playing a role in bone. And so this calcium that's floating around in our blood 40% of it more or less is bound up to a protein called albumin. And so albumin is the most prevalent protein in our serum. And it actually binds and carries a lot of different things. This is going to be another theme that comes up with many of the other biomarkers that we talked about is things that are either in bound form, they're bound to something which renders them physiologically not active. And then there is an ionized or a free form of calcium, which is about 45% or so. And that's the physiologically active form. That's what does the active physiology of calcium, and then a tiny fraction is bound up by other ions and things like that in the blood. And so when we just take a blood calcium measurement, now when you zoom back out, you realize, okay, I'm measuring a tiny fraction of the amount of calcium that's in this person's body, right? 1% or less that's swimming around in their blood. And when I measure it, I'm measuring all of that

calcium, the bounce stuff that's not really doing anything other than being kind of in a storage forum carried around on albumin, the calcium that's bound up to other ions and then the about 40 to 50% or so that is ionized. That is like actually doing the real thing. So it's like a fraction of a fraction of a fraction of the total body calcium that we're measuring when we do a blood measurement. Not only that, but this blood test when we measure it, it can be affected by a lot of different things. So since a substantial fraction of calcium is bound to albumin, that means your albumin levels can influence the calcium number that comes up on the test. If you have very low albumin levels, your calcium is going to look low. It can be affected by your hydration status. That can also impact you know, the concentration of calcium that comes out on that test. It can be impacted by phosphorus levels. It can be impacted by blood pH and as you probably know, blood pH is pretty tightly regulated. But another consideration is, hey, if I draw your blood, and I don't get it to the lab relatively quickly, metabolism is ongoing in those living cells, and the pH of that sample is going to change. So if I don't run it quickly enough, the pH change that can happen can influence the calcium measure that comes out as far as the ionized amount of calcium, the physiologically active stuff, it can make it artifactly erroneous. So these are things that are not appreciated by a lot of folks who do not, you know, spend their day jobs interpreting clinical lab testing like this. I don't necessarily claim to be an expert in like nutritional biomarkers as a topic of its own, but rather, in the clinical application of these tests in you know, day to day medical decision making and things like that. So there's a ton of things that if you measure a number, and then you just compare the number to the reference range and try to do something that seems to make sense, you're probably going to go wrong. And that's really what I see a lot of people maybe who go out and get their own labs done, they might get a lab test done, it'll get flagged as like red or something, they'll compare it to the reference range, and they'll say, oh, that probably means I need to supplement or something like that. And it's like, way, way more complicated than that. So

what when it comes to regulation of this tiny fraction of a fraction of a fraction of body calcium, that's swimming around in the blood that plays all these really important roles, it is so critical that it's tightly regulated, because if your calcium levels that that, physiologically active calcium decreases, you can effectively develop what's called hypocalcemic tetany. Like your muscles, you have uncontrolled muscle contraction, and it's called like tetanus is kind of like this, what it's describing there, if your calcium levels drop, and then at the other end of the spectrum, if they get way too high, you can get severe weakness, and all of this stuff can also impact nerve conduction, it can impact your heart rhythms, all kinds of things can happen. And that's all obviously undesirable, and would be evolutionarily unfavorable. So fortunately, we have these mechanisms through parathyroid hormone, PTH and vitamin D, which are kind of overseen by these calcium sensing receptors that we have in our parathyroid glands, and in other tissues of the body, that keep calcium really tightly regulated, effectively independent of the calcium in your diet, more or less, in like the medium to even long term for most folks. Even, you know, if you're not taking insufficient calcium, then parathyroid hormone will just be prompted to hey, let's just pull it out of your bones, for example, to maintain a normal blood calcium level, because your body would prioritize maintaining a blood calcium level that's normal over your bone health appropriately so given all of the other important physiologic roles that calcium plays. So it's like really difficult to like eat your way to high or low blood calcium levels because of this tight regulatory mechanism that's in place. And as a result, when you ask that question of, hey, what's the relevance of serum calcium for bone health, I won't say it's not relevant, because in the diagnosis or evaluation of somebody who has bone issues or osteoporosis, you should measure a blood calcium measurement. But the way that it is interpreted might seem paradoxical, because it's like, hey, if you have osteoporosis, and I measure a blood test, and I find that your calcium levels high, I'm actually more concerned about that person, because it probably

reflects that they have inappropriate hyper parathyroid activity, their parathyroid is overactive, maybe they have a benign tumor in there or something like that, that's cranking out this parathyroid hormone and it is inappropriately leeching a whole bunch of calcium out of their bones when they don't need to be doing that. And that might be the source the cause of their osteoporosis, I go cut out the tumor, or have a surgeon do that, because I'm not cutting that out. And then the issue will be fixed after that. So it's like, if I told you that, hey, you probably don't want to have high calcium levels, you know, that situation, because it probably reflects some underlying disease process, right whereas the overwhelming majority of people who have osteoporosis are probably going to have pretty normal serum calcium levels. If you flip that, and you look at another potential biomarker, you could check urinary calcium. And that is has some potential value in this situation, because if urinary calcium is high, then that might be another indication that somebody is inappropriately wasting calcium. But now you're thinking about measuring a different kind of tissue compartment so to speak a different area of the body that has its own nuances of interpretation, and things like that. So hopefully, that was a, you know, understandable, but summary of a quite complex topic.

DANNY LENNON: Yeah, there's a number of things. I'll do a very quick recap, because there's a few things that I didn't want to get into. So one of the things here that you mentioned is in relation to calcium homeostasis, because we have this kind of tight control of serum calcium levels. Therefore, that is, number one, not really a good reflection of dietary intake. But beyond that, then you can have various different types of misinterpretation. If someone goes and gets a test, like you said, they see serum calcium get flagged up. And if number one, it is within normal reference range that doesn't really tell us anything much about their diet but number two, if it does something show like, oh, this is a low serum calcium, then you shouldn't go and think, oh, I'll just take a calcium supplement, I'll be fine. It's probably much more of a serious issue. And vice versa the example with osteoporosis, where

we see something paradoxical, like high serum calcium is actually reflective of a problem as opposed to a good thing. So again, accurate interpretation. I think one of the big things that you were also getting to in relation to interpretation is not looking at any of these things in in isolation that a proper interpretation is couched within the context of other biomarkers as well as patient's symptoms, and probably a variety of other things. And that gives a kind of more global evaluation of what's going on, as opposed to what is this marker and what is a normal reference range.

AUSTIN BARAKI: Yeah, yeah, I would say that's pretty much accurate. I mean, a lot of this comes back to some of the basic principles of testing in general, which I know we hammered in the last podcast, and we don't necessarily need to revisit, but as it pertains to nutritional biomarkers in general, you know, you think about like what would I want out of a good nutritional biomarker. You'd want it to be, you know, pretty sensitive to variations in dietary intake and in order for that to be the case, you probably want it to have like a relatively short half life. You'd want it to be unaffected by other diseases that may be present, or other physiologic states that can influence this level. There's a bunch of other things that I think Alan could probably speak more to on, like what you'd want out of a really good nutritional biomarker and this, as well as many other ones that we'll talk about, do not meet that criteria. And so you would go wrong, if you tried to interpret it as a nutritional biomarker when really, it's not that at all, it's playing a much more diverse physiologic role and is tightly regulated for that reason.

ALAN FLANAGAN: That point is really important that they're not neutral. Although calcium is a nutrient, you know, serum calcium is not necessarily a nutrient biomarker, because there's a number of characteristics that we would want to satisfy for it to be that. So it may, you know, also be a nutrient in the diet. But that measurement does not necessarily qualify or validate as a nutritional biomarker.

DANNY LENNON: And that might actually be a good topic to delve into in a moment, one kind of parallel with something you've talked about recently, Alan, that maybe you can elaborate on just as another example, for people, when Austin discuss the consideration of the tissue compartment that we're looking at, you've kind of talked about this in relation to linoleic acid and we're kind of we're trying to piece through the literature here of considering the differences if we're looking at linoleic acid as a percentage of it showing up in fatty acids or fat tissue versus in plasma versus in whole blood. Can you maybe just get into that as another example, for people of why we're seeing differences and why it matters, what compartment we're looking at?

ALAN FLANAGAN: Yeah, so So for nutrition biomarkers, we want the specific measure to be an indication of actual nutrient intake, or certainly or nutrient status that relates to diet. We tend to classify nutrition biomarkers into two broad classes. One is a recovery biomarker, and the other is what would be called concentration biomarkers. And they both are to an extent what they say on the tin. So a recovery biomarker is a biomarker that is recovered usually in urine, and they are relatively few and far between. So you can measure energy expenditure using doubly labeled water, it's very expensive, you need to collect everyone's pee, but they basically drink a stable isotope labeled water, and then you collect all the pee and you can basically analyze that and get an estimate of energy expenditure. Sodium in the diet is primarily there is minimal losses through feces or through sweat despite people kind of often over emphasizing the sweat effect. It's it's not a huge amount. So up to kind of 95, 99% of sodium is going to be excreted in urine. So if you collect all of the urine excreted by an individual over a 24 hour period, you can get a good estimate of sodium intake. So their recovery biomarkers and there are a number of other so potassium can be iodine, for example, so there's a number of them, but they are relatively small and number of validated recovery biomarkers. Then we have concentration biomarkers, which again, is exactly that we're measuring the concentration of a particular biomarker in sometimes serum or blood, we can

measure in red blood cells, for example. There's different compartments within you know, blood that you can measure you can look at, say for example, cholesterol ester content, or phospho lipid content, and then you can measure adipose tissue. There's two ways of doing that. In your sample you can just explore As whatever, let's say, to keep with the linoleic acid example, we're interested in measuring linoleic acid levels in adipose tissue. You can express that as the absolute level of linoleic acid, say in grams per 100 grams, or you can express it as a percentage of all fatty acids present in your sample. And there's a number of factors that are really required to be met, in order for a biomarker to be a good nutrition biomarker. One, Austin's already mentioned his sensitivity, you want it to actually correlate with dietary intake. So as an example, saturated fatty acids are not good biomarkers of dietary saturated fat intake, because we can synthesize those fatty acids internally. And we could also create those saturated fatty acids from conversion of carbohydrate. So you're not really even sure whether the saturated fatty acids that you could be measuring would in fact even be a reflection of dietary fat intake, let alone saturated fat. And then we want specificity. The actual biomarker that we've measured reflects the nutrient of interest. So you don't want something to undergo extensive metabolism in order to, you know, essentially, that what you could be measuring is not necessarily reflective of the compounds that you're interested in. A good example of that is, for years, people questioned whether what they were measuring as far as poly phenol intake or flavonoid intake, could even relate to diet because you know, that such rapid metabolism, they were half life of maybe 90 minutes, how could this add up to chronic effects. But it turned out that what really the exposure of interest was was the metabolites of these compounds that were being converted and then absorbed, and they stay in circulation for up to 48 hours. So measuring the parent compounds, you weren't getting a specific reflection of the exposure of interest. And then there's other factors as well, bioavailability, you actually want that to reflect, you know, levels in the body correlate with,

you know, levels in diet, such that you get this increase and increase. But then the last one, which is important is time integration. So, different compartments will give you different reflections of dietary intake. So if you measure red blood cell levels of fatty acids of linoleic acid, for example, red blood cell turnover give or take around 120 days. So the levels of fatty acids in red blood cells will be if you're measuring in red blood cell phospholipids, for example, is generally considered to reflect that period of dietary intake. So give or take about three months. Serum is much more rapid. So serum may only reflect three to four days of previous dietary intake. If you measured cholesterol serum. cholesterol esters, it could reflect maybe two to three weeks. And adipose tissue is the longest component tissue compartments, sorry, as far as reflecting dietary intake. So adipose tissue can reflect up to one to two years of habitual diet. So these are obviously quite different and so what you know, it's important even that studies try and compare to see, well do these tissue level in different compartments are they even comparable? As far as you know, research goes, if you're going to do a meta analysis, are they are they even comparable generally, for something like linoleic acid because we cannot produce it in the body, we need a dietary source. So linoleic acid will correlate reasonably if you measured it in red blood cell phospholipids and adipose tissue, they would both reflect dietary intake to a reasonably good correlation. So there are a number of factors for a nutrient biomarker that we obviously want to assess. But it's very important that relative to the compartment that you're measuring, is going to give you different interpretive information in relation to dietary intake, as far as a timecourse goes. And so you know, you can then look then as a percentage of fatty acids, and you can see that, for example, higher proportion of linoleic acids in adipose tissue, or higher proportion in red blood cell phospholipids correlate with certain health outcomes. And that can obviously then add to your total picture of evidence because we know that it is quite a good reflection of actual dietary intake.

DANNY LENNON: So if we take one of those recovery, biomarkers and sodium excretion in the urine is a good one, because we've talked about it recently, as a kind of really good measure of dietary intake. And maybe if we kind of contrast that with something like a serum measure of sodium and again, another probably example where there can be misinterpretation, and I know you and I also have talked about how kind of potassium we can pull in here in a similar vein, can you maybe touch on some of your thoughts in around sodium, and then that contrast between these different types of measures and potential for people to have misinterpretation?

ALAN FLANAGAN: Yeah, sure, I think that a good summary statement here would be the reason that urine sodium is a good biomarker for nutritional intake is the same reason why serum sodium is not because variation in urine sodium is part of what allows your serum sodium to remain relatively constant. But sodium is one of the main extracellular ions that we have in our blood, and it's a cations positively charged ion, about half of it, of our total body sodium is in that extracellular fluid. That tiny amount only about 10% is inside our cells and then about 40% is effectively locked up in our bones as well. And these gradients of sodium that we have across our cell membranes, you know, between extracellular where it's mostly found in a tiny amount intracellular is maintained by our sodium potassium pumps. These are on effectively every cell in our body and they maintain these really important gradients of ions across the cell membrane, potassium, actually goes precisely the opposite. It's relatively low in the extracellular fluid, and it's much much much higher inside our cells. So like 99% of our body's potassium is all inside our cells and it's there for a very important reason. So sodium and potassium are kind of like maintained in a segregated fashion for a variety of important physiologic reasons. So sodium is being the main extracellular ion that we have, it plays a really major role in maintaining our plasma volume, our extracellular fluid volume, because as you may have heard, or it's almost like lay knowledge that water tends to follow salt, and in the body and so it is the major contributor to the osmolality of our plasma osmolality

just being a chemistry term for the amount of solutes or particles that we have in our in a given amount of fluid. One of the main reasons sodium in the blood is so important because it influences where water goes. It influences the osmotic movement of water into cells and out of cells, and if water goes into cells, or out of cells that can influence the size of the cells and the tissues, and it can therefore influence their function. And so that's part of why when serum sodium levels get really low, for example, water flows in a particular direction and can cause problems with tissue function, often neurological tissues, our brain, nervous system function, and vice versa, when serum sodium levels get too high, and those are undesirable outcomes. As a result, it is extremely tightly regulated by a variety of mechanisms to include a thirst mechanism that makes us drink water to keep that serum sodium from creeping up too high and then we have other hormone and kidney related responses to maintain that. So the renin angiotensin aldosterone system plays an important role in this and antidiuretic hormone or vasopressin from the pituitary gland also plays a role in this. All of this is kind of master regulated by the kidneys in the hypothalamus. And so low sodium in the blood effectively indicates an excess amount of water in the body, not typically a lack of sodium. And conversely, high sodium levels in the blood indicates a relative lack of water or a failure to drink for some reason. And so when I see a patient whose sodium level is high, I'm having to figure out okay, why are they not drinking? What's the deal here, there's almost always an identifiable explanation for that. And so for these reasons, it is exceptionally difficult to make significant changes to your blood sodium levels through dietary means. There are some very interesting and sometimes unfortunate case reports one that comes to mind was a soy sauce drinking competition which I would not recommend. Somebody made them fatally hypernatremic. They drove their serum sodium level up through the roof and died as a result because that results in things like seizures and very problematic so do not engage in a soy sauce drinking competition. But shy of that silliness, just the regular diet. You know, the reason this came up in

our in our prior conversations is because, you know, we talk about public health nutrition quite a bit and how in general, you know, a pretty wide swath of the population tends to consume diets that are relatively speaking high in sodium content and low in potassium, that plays a role in a variety of health outcomes, cardiovascular health, blood pressure, issues like that. But the where you could go wrong is if you hear that and you say, okay, well let me get my blood checked into my sodium and my potassium levels are good then I'm probably in good shape and my diets fine something like that, where that tells you again, absolutely nothing about your diet. It is very hard both to manipulate your serum sodium through dietary means shy of issues with your water intake if you're drinking way too much water, your sodium in your in your blood go down. If you're not drinking nearly enough water, it'll go up. But just from diet itself, the actual like sodium or salt content in your diet very unlikely to cause substance like significant arrangements, our body, our hypothalamus and our kidneys are a lot smarter than we are on that front. And similar with potassium, diets that are low in potassium from fruits and vegetables and things like that, that we tend to recommend frequently as part of diets for promoting health and improving blood pressure regulation and things like that will also not be reflected in your blood potassium levels. Those are equally extremely tightly regulated. Like I said, 99% of our potassium is inside our cells, which is not even what we're measuring. When we measure a blood potassium level, we're measuring the potassium that's floating around in the bloodstream, outside of ourselves. And so potassium is so important, even a shift of you know, 1% of potassium from inside the cell to outside the cell would be enough to kill you immediately by stopping your heart. So it's like that important that it's regulated very tightly and your body will not allow you to drive your potassium up through dietary means, unless you are profoundly stupid or if you have significant kidney disease being another common mechanism of how people can end up with high high potassium levels. But in general, you know, it is not at all going to be reflective of your dietary

intake in general whereas your urine measures your recovery biomarkers on that front will be much more useful on that front. Urine electrolytes effectively don't really have “normal ranges”and part of why they don't really have normal ranges is because we prioritize maintaining normal ranges in our blood, and we will manipulate our urine composition as needed to maintain normal blood concentrations.

DANNY LENNON: I think that's a really important point because it actually ties in much of what we've discussed previously, particularly in that sodium episode of why something like a 24 hour or even better multiple 24 hour measures of sodium excretion in the urine are so good for assessing dietary intake is exactly the point you made that because of that, tight regulation of sodium homeostasis and blood levels, that is the exact reason why. And if they weren't tightly regulated, then excretion doesn't tell us all that much. And so reconciling those two things is actually really useful, considering not only what a serum measure means in the context of clinical settings, but in also thinking of why we have certain measures like urinary excretion being so valuable for dietary assessment, right.

ALAN FLANAGAN: And you can also validate these biomarkers as well for sodium for example, or even for it in because creatinine concentrated excretion is pretty much constant across the day. Like in any given age group, it can change with age, but for a given age group, creatinine excretion is pretty much constant. So you can validate the accuracy of your sample collection, by measuring creatinine in your urinary samples and then you know, whether this was a complete sample or not, and then likely to reflect, you know, true intake for that day. So, you can often see papers that have looked at iodine status, for example, will often express it as a ratio of iodine to creatinine. But for sodium, that's been invaluable, because, particularly for the “J shaped curve bro!” this, if you look at some of the studies that have suggested, you know, much higher sodium intake, there's one or two older studies as well, that suggests that these high sodium intakes weren't correlated with anything. But you actually look at the validation of sodium excretion in those cohorts and like it

was around, potentially only 50% of samples were complete. And that could be deduced by looking at the creatinine content of those samples. So, you know, it's that extra step of validation for nutrient biomarkers is really, really important. And it's why for all of the continued interest, and there should be continued interest for nutrient biomarkers. Ultimately, the very well validated ones are still relatively few and far between if we consider the total spectrum of vitamins and minerals that we would actually be interested and fatty acids and amino acids that we will be interested in the very good biomarkers that genuinely do reflect dietary intake and could be measured as such, you know, are are still fairly, you know, fewer and far between.

DANNY LENNON: One of the topics that I wanted to dive a bit further into was, again, this idea of certain markers may not mean what people think they mean. And one of the things that you've talked to me, before we were recording, Austin, is in relation to this idea that many nutritional biomarkers, in the context of when someone is sick, or severely inflamed because of a sickness, for example, are basically uninterpretable, I think, was maybe the phrase you used. And you talked about this acute phase response and how that impacts things like say CRP, but also then things like ferritin was an example you gave that can potentially go up when people are inflamed. And then on the flip side, we have these negative reactions and one example you mentioned around lipoproteins, which is kind of quite relevant to some of the nutrition stuff that we've recently mentioned and Alan's piece on low cholesterol levels and increased mortality and investigating that association. One of the ideas mentioned there was exactly along these lines with this unsuspected sickness phenomenon where we have the metabolic consequences of an illness or an undiagnosed disease causing in the case that Alan was discussing a drop in LDL cholesterol levels. But that can happen in other cases. So can you maybe just describe that idea of this acute phase response and we both have things that are positively impacted and negatively impacted, and yet do that in probably a much more eloquent sense then I'm able to do.

AUSTIN BARAKI: Yeah, I'll do my best. So obviously, you know, we come across a variety of physiological stressors over the course of life be it illness, or a traumatic injury, or any number of other things that can happen to us. And our body has effectively this kind of coordinated physiologic response that can kick into action. In particular, this acute and potentially chronic inflammatory response that can happen, the acute inflammatory response when we have say, an infection of whatever variety or a traumatic injury or something like that is pretty beneficial, pretty adaptive in general, for in most situations. Of course, it can spiral out of control, like in uncontrolled sepsis and things like that. And we also have this chronic inflammatory state that we can be in which is less often beneficial, more often pathologic or maladaptive in a lot of situations. But what happens in this inflammatory response is we have, you know, immune activation, we have alterations in like neuro, hormonal mediators, a bunch of different things that are all part of this kind of coordinated response to deal with this stressor. And most of the proteins and other mediators that are found in our blood are synthesized by the liver. And so we have this, as you mentioned, this acute phase response, which is kind of a fancy term for this coordinated, you know, response that we have to these kinds of insults, where a variety of things will be, will increase in our blood, production will ramp up as part of that one of the very common, more well appreciated one of those proteins is called C-reactive protein, which we actually use clinically as a marker of inflammation. It's not especially specific for a particular pathologic diagnosis, but it's more reflective of a general inflammatory state. Other things, as you mentioned, ferritin, there are like amyloid proteins, a whole bunch of there's a lengthy list of proteins that we find at mild, moderate, and extremely, you know, increased concentrations in the blood in the face of some sort of an insult, injury, inflammatory process like that. And it doesn't have to be, again, profound illness. It could be something, you know, there are milder versions of this, like in metabolic syndrome, diabetes, obesity, if somebody has a surgery, or something like that all these things can drive a

bunch of these kinds of changes that are detectable in the blood. And conversely, to those things that increase, we also have these negative acute phase reactants or these negative responses where certain things will decrease in concentration. And they decrease for a variety of reasons. Some of them are probably decrease due to decreased synthesis. There is probably like a reprioritization of the liver of like, what's most important for me to make with limited resources right now. But there are other things as well. There are probably also some renal and gastrointestinal losses of some of these things that happen. And then very importantly, there's probably also, some of these things actually leave the blood circulation and enter the tissues. For example, if there's like a local injury site or something, some of them might actually leave the bloodstream and get into the tissues to like, do their business there. But ultimately, that result may be, hey, when I measure the concentration of this in the blood, it might decrease. So there's a variety of things that either go up or go down and they may do this for a variety of reasons. The things that go down include some of the things that you mentioned. So various lipo-protein concentrations may decrease. Albumin is extremely relevant here. As far as albumin, as a reminder is that protein that I mentioned earlier, it's the most prevalent protein that we have in our blood. And it is really important because it serves as a carrier. So many different things, bind it medications, ions, vitamins, things like that will bind on to albumin for transport around the blood. And so if albumin concentrations decrease in this situation, it can also result in all of those other things looking low when we measure it. And so there are a variety of things that when you say I work primarily in inpatient hospital setting acute care with, you know, people with acute illnesses, and maybe, you know, sometimes multiple underlying chronic disease states and if I want to test something, I have to think to myself, okay, what is this going to be useful? Is this going to tell me what I think it's telling me? Is it going to allow me to act with confidence? Or is it going to be something can I predict that oh, this test is going to be screwed up because there's, you know, likely to

be an acute phase response because of what their acute illness right now? Or could it be deranged because of their chronic disease state, maybe they have cancer, and that might affect some of these things. Maybe they have chronic, you know, HIV infection, uncontrolled diabetes, cardiovascular disease, any number, you know, chronic kidney disease can really mess with a whole bunch of things. So there's a variety of things that are deranged in various directions. And it can add another layer of complexity to interpreting some of these labs, and especially some of these, you know, things that we might otherwise think of as, you know, nutritional biomarkers. So measuring certain minerals in the blood be it zinc or copper levels or certain other things that can get really off in some of these situations. Really importantly, as well, certain hormones can get screwed up. So thyroid hormone, testosterone, things like that, in the setting of some of these things become much less valid for, you know what we'd otherwise normally use them for and that can lead to erroneous, you know, conclusions. And vitamin D is, you know, one of my pet topics that I end up ranting about too much. But this is another one that tends to go down quite a bit in both acute illness and in chronic disease. And just to illustrate why this topic is quite important and relevant, especially at this moment, is you can go out there and find piles of papers, correlating patients who gets admitted to the hospital for COVID, for example, and those who have very low vitamin D levels have worse outcomes. And so what you see are functional medicine folks, biohackers, and all the other folks who are lumped in with that they hold up these observational papers that correlate low vitamin D levels and this is 25 hydroxy, vitamin D, which is kind of like our body's circulating kind of storage form of vitamin D. It's actually not even the active form of vitamin D that we have in our blood, because our body again is smarter than we are. It won't let us supplement our way to vitamin D toxicity outside of there, we have to try hard to do that. The activation of Vitamin D is regulated. But these levels go down in the setting of chronic diseases and in acute illness. And so if somebody is quite sick, it is entirely

unsurprising to me that their levels will be low and although I don't know exactly how validated this is, I would not be surprised to find that the sicker that person is from this, the lower those levels will be suppressed down to effect essentially undetectable levels. And so the conclusion that's drawn is see, if you just take vitamin D get your levels up, right, you won't get admitted to the hospital, you won't get sick. This has not really been convincingly shown. There is even a living a systematic review at Cochran right now that is following the evidence on this and haven't really found convincing enough evidence that this is going to be like the miracle cure to prevent severe disease or hospitalization. But you can see how compelling of a story that can be if you don't bother to differentiate from cross sectional, observational studies looking at sick people and finding the entirely unsurprising finding that sick people have lower blood levels because of this negative acute phase response. But then you have to contrast that to prospective randomized interventional trials that failed to show that massive have an effect as far as if I supplement you with this, either pre or during illness, that this is going to markedly influence your outcomes. This gets even more complicated as far as the regulation of vitamin D circulating in the body, which is you know, we don't even have to get all that far into but like I said, it's activation is pretty tightly regulated by things like parathyroid hormone, which we mentioned earlier, the kidney and similar to some of these other things Vitamin D circulates in the blood on something called vitamin D binding protein, which we do not measure clinically. I'm not even aware of too many studies that bother measuring it in the research setting either. And there is variation in vitamin D binding protein levels based on genetics. So certain ethnicities have been reported to have different levels of this inflammatory processes, cortisol, hormone variations, estrogen, things like that can influence vitamin D binding protein levels, which will then influence the amount of vitamin D that you measure in the blood. When we did our vitamin D discussion at Barbell Medicine, I found some very interesting case reports of one human family that was found

they had a genetic mutation that effectively deleted their vitamin D binding protein. So they had effectively undetectable vitamin D levels in the blood. But otherwise were apparently completely healthy without any evidence of deficiency when they were consuming a normal diet. And so it's kind of interesting, when you think about hey, this like protein binding thing, whether vitamin D binding protein or albumin or any other protein that carries stuff around, it's actually real important and underappreciated when people try to interpret the meaning of these things, especially when those proteins tend to get deranged up or down in the setting of this acute phase response.

ALAN FLANAGAN: There, there's something that comes to mind there in relation to that, which is another darling of, shall we say the kind of functional medicine or nutrition space and it's in relation to zinc. And zinc is like a fascinating like nutrient and zinc, you know, roles in the body I think nearly 10% of all human proteins bind with zinc. So it has this myriad physiological functions but, you know, in its in its three classifiable forms, you know, you've immobile zinc, which is you know, non exchangeable and nonreactive, and then the mobile reactive zinc, and then the reactive pool or freezing, but that's like the least of those we don't tend to have, you know, zinc. It's, like just again, free or floating about. And yet, you'll have these kinds of various, “tests” for zinc status, which are likely just telling you absolutely nothing, you know, exchangable kind of bound zinc in the body or certainly in relation to dietary stasis at all.

DANNY LENNON: Yeah, the vitamin D is again another useful example of points that we referenced earlier of having it couched within the context of what is happening with the patient as well as other markers that are going on. And in this case, noting whether there's an acute infection, for example, if someone's level of Vitamin D is low, that doesn't necessarily mean then the answer is a supplement, in that particular case. So again, it's a reminder of rather than looking at these things in isolation. Vitamin D is an interesting one, in particular, and there was a number of things that I think Alan, you and I had

mentioned, that might be worth delving into here. And one kind of relates to maybe, again, more of like Vitamin D is so difficult to give recommendations on. And I know like, even in like a sports medicine context, Graeme Close's group at Liverpool have done quite a lot on vitamin D. And by the end like they were like, look, it's so difficult to give recommendations because of like, how do we get actual accurate measures compared to what's typically done. We don't have that good evidence really across different types of populations and what that may mean. And then when it comes down to how it's actually used, again, we're kind of still up in the air and a lot of these questions. So trying to give, like blanket statements on typical supplementation, and therefore, specific blood level is very difficult to do. And one of the things that we've pondered before is that we see differences in kind of those recommended levels in North America and Europe. And I know, this is a point that you were interested in getting into Alan so maybe can you kind of mention a kind of introduction into those differences if people haven't heard and then we can kind of get into it from there?

ALAN FLANAGAN: Well, yeah, it's been one of the raging debates in the academic literature on vitamin D, and it relates to measured 25 hydroxy, vitamin D levels, as Austin said, that typically is what is going to be the actual measurement, and that will be taken to then reflect vitamin D status, so to speak. There has been a variance in recommendations between what you would get with various regulatory bodies in North America versus in Europe. So most of the North American Public Health bodies or the various kind of, you know, associations or regulatory bodies, tend to recommend over 75 nano mil per liter as being sufficient. In Europe, that would be over 50. So between 50 and 75, one of the primary justifications given for that is that over 75 nano mil per liter, 25 hydroxy Vitamin D is where you tend to see the maximal suppression of parathyroid hormone. Now, there are groups that debate that you want to maximally suppress parathyroid hormone, it follows a rhythm. Its rhythmic pull, you know, kind of oscillation might actually be quite important for bone health.

And so there's all this kind of nitty gritty debate that there's possibly even a separate kind of concept in itself. But that's where you get this delianation in the recommendations. And but it has a lot of relevance for research findings, because you can have studies, if they're conducted in the U.S. population, intervention trials, in particular, where your participants in both intervention and control groups have over 75 nano mil per liter of measure 25 hydroxy vitamin D. And then on the other end of that, as we discussed on that podcast, you've got some trials where they have, you know, less than, say 25 nano mil per liter, but they're given a relatively low supplemental dose. Their blood levels don't really come up that much. And the trial concludes, this had no effect on, you know, on any of the measured outcomes, like fracture incidence, for example. So this is kind of a critique that applies to a lot of nutrient exposures and the conduct of nutrition interventions. But I think in relation to vitamin D, it's particularly important. And this discrepancy, as far as I'm aware, between the recommendations is really no further along and being resolved and they kind of seem to have almost set in stone on both sides of the Atlantic without much further scrutiny. And so, you know, as Austin said, you know, that there's likely all of these other factors that, you know, possibly have to be considered within that. But certainly, it seems to be that this justification is well we maximally suppress parathyroid hormone that will be good for bone health because parathyroid won't be acting on bone in the way that Austin described in relation to calcium. But that might really be a gross oversimplification of the relative parathyroid hormone and all of this and it may not really be an optimal public health recommendation. So yeah, I think that's something we'd love to get your thoughts on Austin because I know you discuss a lot of this in the Barbell Medicine vitamin D podcast, but it could be really relevant again.

AUSTIN BARAKI: Yeah, I agree with much of what you said there. I think that basing our recommendation on that is as much of like a surrogate outcome kind of thing as you can get as compared to, you know, having hard endpoints of evidence showing

that, hey achieving this level broadly is going to have this impact, because I can't, you know, I can't help but notice when you look at a lot of these observational studies, cross sectional things, retrospective things that correlate high versus low blood vitamin D levels, with, you know, a bunch of adverse health outcomes. Some of the differences, or the apparent effects that you see in those types of papers are massive. And then you compare that to what you actually see in prospective intervention stuff. And you're like, wait, where'd the effect go? There may in some places still be a detectable effect. And it's also important to look at all the things that you guys have mentioned, that's particularly relevant for like nutrition and supplementation trials, where are they starting from, what levels did they achieve all other kinds of things like that. But still, like when I zoom out, and I look at what little we know about this complex system, I can't help but feel like, you know, we're operating on like, imagine that we're playing in one little sandbox moving piles of sand around compared to like the whole world around us as far as like how complex this system is. And it just feels somewhat trivial. Obviously, there are definitely situations where people can have health and medical complications as a result of severe vitamin D deficiency be at osteomalacia, rickets, things like that, that we fortunately don't see all that much anymore. A lot more often, instead of those like, frankly, malnourished states, or individuals with gastrointestinal diseases that result in fat soluble vitamin malabsorption, and things like that. Outside of those contexts, you know, much of the population that we see are arguably over nourished. And as a result of that, when we see significantly low blood vitamin D levels, the first place that I'm looking at a lot of those folks are okay, what other health conditions do they have that are, that could be you know, interfering with this measurement? Could they have you know, some excess adipose tissue? Could that be influencing their internal hormonal milieum altering vitamin D binding protein levels? Do they have fatty liver disease? Do they have an element of you know, chronic kidney disease? Do they have undetected, other undetected things that could be influencing these

levels, rather than the somewhat simplistic and but apparently compelling approach of measure the level compared to the reference range and supplement to make the number look pretty, which is quite easy to do, right. But in some situations, in some patients, it might be the effect of like, hey, my, like check engine light in my car came on, let me just disable the light and say the problem is fixed. Like, I might not actually be as confident in that kind of a situation.

DANNY LENNON: Before we start pulling into conclusions. Is there anything we haven't gotten to that you think is particularly relevant? Or are there any open loops that we need to close before we start getting into some conclusions?

ALAN FLANAGAN: I wonder what your blood levels of, you know, a range of nutrients would go to if you just consumed liver, every day.

AUSTIN BARAKI: As long as it's not polar bear level, right?

ALAN FLANAGAN: Like I'm thinking vitamin A, you know, iron, you know, it's.

AUSTIN BARAKI: Yeah, yeah.

ALAN FLANAGAN: What to what to measure?

AUSTIN BARAKI: Although, you know, some things would go off the charts. And then some things fortunately, as I said, I think that the theme is that in a lot of these areas, our bodies are smarter than us are, and won't let us cause ourselves a lot of harm, but through substantial blood through a bunch of these tight regulatory mechanisms. I mean, I think that, you know, as far as I don't have a ton of other, you know, real important topics that I think we ought to address other than hammering some of these themes, again, one of which, at the outset, was differentiating between screening and diagnostic testing, and screening, just referring people to the last podcast, like you need to have awfully good justification to be able to go and get testing done without signs or symptoms. You want to have a important health problem with a latent asymptomatic phase that has a cost effective treatment that can modify the health trajectory. That is something that justifies screening. Outside of that, a lot of people get tests

done that they don't actually need to get done in general. And then what happens when they get test done is, of course, just human variation, lab error, a whole bunch of other things might crop up to result in something getting flagged as abnormal. And suddenly, this person might have some unnecessary health anxiety or feel compelled to do something about this result when maybe they would have been better off not getting the test done at all, in the first place which ties into the clinical context of actually doing tests from a diagnostic standpoint, knowing that context, the signs, the symptoms, the other justification for getting a test. And knowing what you're going to do with that testing information. The reason we get these kind of tests in practice is to alter our kind of diagnostic probability, which would then alter our threshold for intervention for action, in hopes that we can alter the person's health trajectory or disease course. And so looking at these numbers, as you've said, a few times in isolation is not the move. You will probably be led astray or make mistakes and just, you know, people being able to get there labs without the training to interpret them with all the complexity that we have just even scraped the surface on in this podcast is an easy way to get led astray, knowing the diagnostic value, the things like the sensitivity and specificity of your test for what you're looking for, knowing the confounders the things that can influence it, for example, is this the appropriate tissue compartment to be sampling? Is there a significant degree of protein binding that I need to account for? Is there a significant effect of an acute phase response? Could that phase, acute phase response be going on to any degree even a mild level in this individual may be due to obesity or metabolic syndrome on the milder end, or more significant inflammatory disease, undiagnosed things, cancer, etc on the more severe end? All of those things can play roles in influencing the number that we get back on a test and knowing how to put that number in context of the patient in front of you. And acting accordingly is a very difficult job. It's why it takes a hell of a lot of training to actually get to that point where you can do it. And we still, you know, people still mess it up, I still see folks who

might come to me saying, hey, I got this test result. And somebody told me, I should do this. And I might disagree with it. And I probably made mistakes of my own in test interpretation at varying points as well, because it's, you know, we're all humans, and we do this, but I think that's why caution is advisable. And really just not assuming that the test is telling you what you think it is, if you don't actually know that to be the case, particularly when it comes to some of these blood measures, as supposed nutritional biomarkers, which they often are not.

DANNY LENNON: Alright. And I think even beyond the ability now for us to get like tests very easily and then the clear pitfalls of like self interpretation followed by self diagnosis, hopefully by this point it's very clear of how problematic that is. But one thing that I think I mentioned to you previously is that maybe even more problematic for people is that if they're going and working with someone who is a functional nutritionist or a wellness coach, who then prescribes them to go and get a bunch of blood tests done to make it look comprehensive and like they're doing something magical, those people are probably not able to interpret that I would say, I would be nearly certain that nearly all of them would not be able to interpret those appropriately. And that's maybe even more problematic, because then the person feels like they're in good hands, that "someone knowledgeable," is taking care of this. And so they're probably going to be even less skeptical of what they're doing. Whereas at least if you're self diagnosing, hopefully some part of your mind is like, hey, maybe this might not be a good idea. And if I don't feel better soon, I should probably go to a doctor. Whereas if you're being taken care of number one that could have really bad consequences, as well as in the meantime wasting other resources like your mental energy, health, anxiety, your money, etc, on these recommendations of a wellness coach who is prescribing you labs when they absolutely should not be.

AUSTIN BARAKI: And those people are often selling you supplements on the other end of that lab testing, which is also a major, you know, red, red flag emoji as they say.

ALAN FLANAGAN: Right. Yeah, I believe they're known as protocols.

DANNY LENNON: Yeah, yes. Protocols. Whole protocol. This is about 9 or 10 different supplements involved.

AUSTIN BARAKI: Yeah, it's absurd. You're totally right, Danny, about how you know, doing more things can definitely make it look like you're getting better care, you're in better hands compared to if you come to me and I say, here, here are the like, you know, you're feeling fine. Got no issues right now. Cool. Like, there's probably like a lipid panel and a blood pressure check. Make sure you're up to date on your cancer screenings. And then otherwise, Yeah, you're good to go versus like testing everything under the sun. Because, you know, I just want to get checked and things like that can definitely cause major problems.

DANNY LENNON: Yeah, I don't want to make a judgment call on someone. But if someone is just, let's say, a wellness coach, or what other other title they're using, and don't have appropriate training, but they want to be telling people to go and get a bunch of blood tests on that they're going to go and interpret. That's basically kind of this idea of a want to doctor, right? That I don't want to do any of the training, but I still want to do what you try and do and this feeling that yeah, this kind of omnipotent feeling that oh, I actually can do it. I don't need the training, but I can interpret these effectively based on something I've read. Yeah, it's a kind of a strange omnipotence or narcissism I think. Again, I don't want to make any judgment calls on people who are doing that but hopefully none of them are listening to this podcast per se. I very much doubt based on our audience.

ALAN FLANAGAN: Years ago, I measured I was you know starting to become like interested in the, you know, circadian stuff and I ordered like one of these you know, direct to consumer like melatonin and test cases like I'll be really interested to know

like, what my melatonin levels are, you know, and I was like part of my PhD. like, you know, measuring melatonin in a lab like, like how complicated it is knowing how many repeated samples you need. I think I woke up during the night the only instruction was don't turn on the lights and spat into it. But like 2am, so I got like some single random measurement of melatonin at whatever time that was. And supposedly that told me something, you know.

AUSTIN BARAKI: It's like, yep, you were asleep.

ALAN FLANAGAN: Yeah, that was it. It was 2am. Let's thank you. It was dark in my room. That's what it told me. So, yeah.

DANNY LENNON: Yeah fantastic. Yeah, I think on a personal level, we've all done that to some degree of like, oh, and this is kind of how our original conversation came about Austin of like, there's a presumption that well, what is the harm in certain basic testing, right? So what's the problem with me going ordering certain labs, even ones I like, relatively normal, it's even like lipid panels or so on or, like just keeping up to date with bloods and then there's a yeah, people being unaware. And that was the same way with me in the past of being unaware that oh, there's actually potential harms here. It's not a kind of benign thing. And so yeah, my vitriol is very much aimed at people who are making money off people as opposed to any of us who have fell for such things in the past.

AUSTIN BARAKI: Yeah. We've all been there.

ALAN FLANAGAN: Yep. I think as well, just because so many of our listeners are nutrition professionals or medical professionals interested in nutrition, personal trainers, people who read nutrition research, in addition to the kind of general caution that Austin and Danny have have made this also applies to thinking about reading research and so don't assume that because you read a study that says it measures a certain tissue compartment of whatever the nutrients of interest supposedly is, don't assume that that necessarily reflects dietary intake, particularly with Mendelian randomization studies which are just proliferating for nutrition exposures

now, there are like gratuitous causal claims being made. And one thing I would caution for people is with MR studies, if you've read that they measured serum levels of something, well, then the conclusion is not against the nutrients, it's simply against that tissue compartments and that might not even measure reflect that nutrient status at all. So there are take home points here for reading and interpreting and thinking about research as well as how people might apply this and, you know, kind of clinical practice.

DANNY LENNON: Cool. I think that pretty much does us if both you guys are happy to finish it there, we will round off. Thank you everyone for listening into this episode. If you enjoyed this episode, then please share it with someone else who you think might like this particular topic of conversation, or indeed you can share it around on social media. You can tag us if you do. The show notes are available over on the website, we'll link up to anything relevant to this particular discussion that may be useful and more informative. And yeah, with that, thank you again for listening to the podcast and for myself and from Alan and from Austin thank you and