Nicki: Welcome to the Healthy Rebellion Radio. This is an episode of Salty Talk, a deep dive into popular and relevant health and performance news pieces mixed with the occasional salty conversation with movers and shakers in the world of research, performance, health, and longevity. Healthy Rebellion Radio Salty Talk episodes are brought to you by Drink LMNT, the only electrolyte drink mix. It's salty enough to make a difference in how you look, feel, and perform. We co-founded this company to fill a void in the hydration space. We needed an electrolyte drink that actually met the sodium needs of active people, low carb, keto, and carnivore adherence without any of the sugars, colors and fillers found in popular commercial products. Health rebels, this is Salty Talk.

Nicki: And now the thing our attorney advises, the contents of this show are for entertainment and educational purposes only. Nothing in this podcast should be considered medical advice. Please consult your licensed and credentialed functional medicine practitioner before embarking on any health, dietary, or fitness change. And given that this is Salty Talk, we should expect the occasional expertive.

Robb: I'm I driving today?

Nicki: You're driving.

Robb: Okay. Cool.

Nicki: You've got the reins.

Robb: I got the power.

Nicki: You got the reins.

Robb: Welcome back everybody.

Nicki: Yes. Welcome back to another episode of the Healthy Rebellion Radio. This week, we've got a Salty Talk, although how salty did you get?

Robb: Well, I was chatting with Dr. Bill Cromwell about literally all things cardiovascular disease risk, cardiometabolic risk, and I'm pretty good at this stuff and I had to walk briskly to keep up with Bill. So this is going to be an action packed episode for folks. In the Healthy Rebellion, excuse me, we've been talking about the precision health reports. Folks have been going through that both pre and post reset and just a host of different circumstances, getting some amazing insights, oftentimes discovering that they are shockingly healthier after a reset, which shouldn't be entirely surprising, but there are so many questions in this space. Back in 2010, I was of the opinion that so long as you kept insulin levels low, cardiovascular disease risk was a non issue and there you go and unfortunately, it's a lot more complex than that. There's a lot of different moving parts. Bill is a big fan of paleo, keto, low carb diets, but also recognizes that it ain't the whole picture. There's a lot of... I believe he said that there were 79 known genetic polymorphisms that affect cardiovascular disease-

Nicki: Wow.

Robb: ... or just lipoprotein status. So the vast majority of people, just cleaning up diet and lifestyle and everything does what they need. It's like Bronto. It provides

you what you crave, but for a lot of situations, there's more details, nuance, complexity. We dig into things like the lean mass hyper responders and really get Dave's thoughts on that.

Nicki: Bill's.

Robb: Or Bill's thoughts on that. Dr. Cromwell has talked with Dave Feldman extensively about this stuff. So he's very well versed in what Dave's theories are on it and Bill fills in where he agrees with that and also where he disagrees with that. We talk about statins, PCSK9 inhibitors, how these may... When and where these things might reasonably be dropped in which, there's actually some, particularly with the way that Bill tackles this, some very, I think reasonable cost benefit analysis that is done here and Bill really does try to leave that as the last stone to turn over and even proceeding that really likes to default to a carotid intimal thickness scan and or a coronary calcium scan. Although we talked about those two in both the pluses and minuses of both of those screening methodologies. So man, it was a lot.

Nicki: But I'm excited for this episode because I feel like it's going to be super helpful for so many people. Even just this last week, one of our friends in jujitsu had gotten some traditional work done from a standard MD, which of course is not the full picture because it's not looking at particle size and all of the components of the panel like the Precision Health Reports panels looks at, and her total cholesterol was high, which as you've said, many times high cholesterol in women, total cholesterol, anyway, I'm assuming other things are in line, can be a predictor of-

Robb: Longevity.

Nicki: ... longevity. Anyway, so this MD told our friend, "Oh my gosh, your cholesterol is so high. You need to go plant-based right now."

Robb: And start a statin.

Nicki: And my friend said, "Well, that's not acceptable. I don't do well on that." And she's like, "Well, then you need to start a statin." She's like, "That's also not acceptable to me." And the doctor didn't even know how to handle. Anyway, so this friend is going to... I gave her the info to how to get the precision health cardio-metabolic risk assessment panel, which will more of a complete picture and then we can go from there. So I do want to say, I'll just say this upfront, that the panel that Rob and Bill talk about in this show for all of you listening, you are able to grab this. Actually, I didn't put the link in here. It's-

Robb: Precision Health Reports.

Nicki: ...precisionhealthreports.com.

Robb: Yep.

Nicki: Okay. And if you use code Robb Wolf, R-O-B-B W-O-L-F, you can get 10% off of the risk assessments. Heads up, that code is only for non-Healthy Rebellion members. If you are a member of The Healthy Rebellion, you have special pricing in there. So this 10% off is just for the Healthy Rebellion Radio listeners who are not also Healthier Rebellion Community members.

Robb: So if you're a community member, dig around in there and we'll get you squared away with an even more better link to that.

Nicki: Yes. Okay. Should we just jump into the interview now?

Robb: Sure. Let's do it.

Nicki: Okay. We'll jump in.

Robb: Dr. Cromwell, how are you today?

Dr. Cromwell: I'm doing well. Thanks, Robb.

Robb: Good to see you, and we are here to discuss a lot of topics related to lipidology cardiovascular disease risk. Clearly you are the pointy end of the spear of the Precision Health Reports process. Can you tell folks a little bit about that? You've been on the show before talking about Precision Health Reports and we've been digging into this more within the Healthy Rebellion, but just let folks know a little bit about what that is.

Dr. Cromwell: Yeah. Some context for Precision Health Reports, what we're really interested in is trying to identify people in what we would call a dysregulated state. And if you think about it, health and wellness is what we aspire to and under normal conditions, we can maintain wellness with good therapeutic lifestyle, diet, exercise, and that's really a testament to the fact that we're a very complex, amazingly integrated and resilient organism. We can do a lot of things within boundaries and have good health. And the question is what begins to escape the normal boundaries of good health? What does dysregulation look like, especially as it relates to diabetic risk, heart attack, and stroke? What your listeners are very, very much aware of and some of my patients are becoming more aware of is that there is a sequence of change, a sequence of metabolic events that take place that move us from what would be considered an ideal wellness state to increasingly dysregulated states all the way to very, very abnormal states, which can culminate in frank diabetes, heart attack, and stroke.

Dr. Cromwell: And along that continuum, we've had some pretty blunt instruments through the years to try to identify people who may be trending in the wrong direction. In some cases, we've waited for events to occur, right? So you've had a heart attack. Well, that's not right. I wonder what happened there. Or you wait for people to become frankly diabetic. You've really lost the detection window and more importantly, you've lost the window to do something about it. All right. So then if we start working backwards, in the '70s and '80s as you know, there were some populations that people wanted to follow for a long time to try to understand some of these more proximal steps. Framingham was one of those.

Dr. Cromwell: Basically you take a group of people who you think are otherwise healthy and well, and you just watch them for time and some get heart attacks or stroke and some don't, and then you try to figure out, "Well, what characterized the people who did something bad?" This is where the idea of major risk factors came from. If you had hypertension, if you had high total cholesterol, if you have low HDL cholesterol, if you were smoker, except for these were factors that on a large macro scale defined a subset of people who would be more likely to have problems than not.

Robb: Got you.

Dr. Cromwell: And then this evolved into risk calculators, right? The whole idea with the risk calculator is that you try to take a population and distill it down to the fewest number of factors that would discriminate in a bulk way people with risk or people who have less risk. We had these equations that we used and all of this is still missing the mark. And the mark is that as we become insulin resistant, as we drift into the cardio-metabolic risk sphere, there are many abnormalities physiologically that take place that are not part of just the normal pathway of identification of individuals. What we can do now with much better understanding of the disease, what we can do now with better tools is we can identify individuals where they are, with continuous risk variables to say not on a scale of good, bad, but on a scale of say one to a hundred, where are you?

Dr. Cromwell: And how are you responding to opportunities to make that better? So Precision Health Reports quite simply is a report that takes your history, your labs, the multitude of guidelines and outcome data we have on hand and synthesizes it into a single report that tells you about you. We don't have to try to guess that a thousand people like you, we can tell you where you are, and we want our first key on insulin resistance, your metabolic health, your eight year diabetic risk, your risk for heart attack and stroke. And then we want to see how you improve in critical areas over time as you make good adjustments, diet, exercise, potentially medication, but you don't have to start there.

Robb: Great. That's an amazing synopsis of that and why I am so excited for what you all have been doing. I've been following your work for close to a decade now, and every single time I sit down with you, I think that I knew something and I discover I did not know it. And we discovered that just before we started recording. So a good number of people within the Healthy Rebellion and then clearly outside of the Healthy Rebellion are exploring the Precision Health Reports, trying to get some deeper insights into their metabolic health, their risk for developing diabetes or risk for developing cardiovascular disease, and as luck would have it, given that those are incredibly complex processes, there's about a million different questions and situations that pop up around that. So if you don't mind, I'm going to start working my way through this list of questions. They are fortunately, or unfortunately not really categorized in any specific way.

Robb: So maybe a little bit of a grab bag, but man, I'll just start at the top and then start working our way through. When would you consider a statin in general and why not default directly to a PCSK9 inhibitor? There does seem to be some concerns around worsening insulin resistance with statin. Some people develop some neuropathy. Again, my understanding of this, I try to stay on top of it. Clearly don't stay on top of it as well as you do, but just from a 30,000 foot level, the PCSK9 inhibitors seem to be both remarkably effective at reducing cholesterol and lipid proteins and also seem to have a bit more of a benign say like a risk profile, but what are your thoughts on that? When would somebody initiate a statin and then why a statin versus a PCSK9 inhibitor?

Dr. Cromwell: So the bigger question is when are medications to be considered and what constitutes a good candidate for medical therapy?

Robb: Great.

Dr. Cromwell: And that's really where the guidelines started to change in 2013. Prior to 2013, we had iterations of the Adult Treatment Panel or ATP guidelines. There was ATP I, ATP II, ATP III, and these were very centric on the idea of lowering LDL because population studies look relatively better if you were relatively lower, and that was the currency of the realm. You just check lab work, if you don't like what you see, fix it. You fix it by addressing underlying problems or using medicines like statins. So fast forward to any number of studies where we started to stub our toe a little bit on the outcomes. One of which was, "Okay, good. Everybody who took a statin get significant reduction in cardiovascular risk."

Dr. Cromwell: No, there was relative risk reduction, but people still had events. Okay. Second, did everybody who's under statin do well in terms of adverse effects? No, there were people with adverse effects and really the inflection point in that came with the miracle study, which was an interesting trial with people with acute coronary syndrome, and the intervention was 80 milligrams of atorvastatin lipitor. Now what's really interesting is that if you were in the midst of a heart attack or a near heart attack, you're a very different person than somebody walking around with stable coronary disease. So what we can say in the ICU and the cath lab, somebody who has a heart attack and you're trying to do the right thing for them, they are in an incredibly high risk short-term state. Their 30, 60, 90 day morbidity, mortality is very, very high.

Dr. Cromwell: So what to do about those people was the backdrop of the miracle study. And one thought was, "Well, maybe we could give high intensity, high dose statin therapy and these people, and they would do okay." And they did. They actually did remarkably well at 30, 60, 90 day funnel timeframes. So motivated by that data, there was a knee jerk reaction that said, "Then we should just use high-intensity standard therapy out of the box for everybody." And what we did was in a really short period of time, we went from a measured start with a modest statin to, "I got a big tool and it's for you." And everybody got the big bang wide off. Well, what do we know about high intensity statin therapy? It has more adverse effects. No doubt about it. We suddenly put people in a position where having been statin naive, they get exposed to high intensity statin therapy very early in their treatment course, and there was a real increase in the number of adverse effects people complained about.

Dr. Cromwell: So I think that's a real criticism of what statins do or don't do, and then how do we try to react to that? The second point of reference was these combination therapy trials. So statins do okay, but there are still residual risks. So should we give another therapy on top? It makes sense. So you know that there's niacin out there and there were niacin and statin trials with smaller numbers of patients that looked very promising. So we thought, "Well, maybe we can add niacin to a statin and that would give us better results than just the statin alone." Well, then we tested that in large studies, aim high, HPS to thrive, and unfortunately, those did not perform. There was no additional benefit in trials, properly powered, very large, adding niacin to a statin. Okay? Well, that was the learning. Same thing happens with fibrates. Fibrates by themselves in the Helsinki Heart Study reduced cardiovascular events.

Dr. Cromwell: When you add a fibrate to a statin in large trials, it did not significantly reduce pre-specified primary cardiovascular events. So now we've got a problem. Not everybody on statin does well either in terms of benefit or risk, not everybody on combination therapy does as expected, and yet we have guidelines that

we're going to advise who gets medicine and why. And that's running into 2013. In 2013, then I think an appropriate reflection was made on what do outcome trials teach us? And what they teach us is there are subsets of patients who do better when exposed to a statin than others in terms of outcome benefit.

Dr. Cromwell: So they came up with four treatment groups. If you have an event already or arterial plaque, that's one, if you have very high LDL cholesterol over 190, that's two, if you have diabetes, 40 to 75 years of age, that's three, and then if you have what's presumed to be very high risk because of an established calculator, which shows that you're over 20% risk and in 10 years in the Framingham Equation or over a different threshold with the pooled cohort equation, but basically you're focusing on those people. And the reason you're focusing on these people is because the unasked question in the room is what happens if I do nothing? What's the natural history of doing nothing? And I laugh because my fellowship, that was one of the questions that I remember many years ago that my mentor came to us with one day. And his question was, "Why would you treat this guy with a medicine?" And we said, "Well, what's the disease?" It doesn't matter. What's the medicine? It doesn't matter. Well, what's the answer? And the answer is what if you don't do anything?

Dr. Cromwell: If you don't do anything, if the outcome is poor, then you have a reason to treat. So back to the ATP guidelines and now the ACC guidelines, leaving people where you find them shouldn't motivate our conversation and what we think are options for consideration. If I leave you where I find you and the risk is bad, then I shouldn't leave you where I find you. So that's the first question of who gets a statin, who should we consider? Look at the natural history of the disease and ask yourself the question, is there a negative outcome if we leave you there? So that defines a smaller group of people that we need to consider it for therapy. So the second thing then is with statins, are we treating numbers or are we treating people who have risks or known plaque in order to reduce their events in the future? And I think it's the latter. We're going away from treating numbers to treating disease. And that's something I'm sure we're going to dive into in a few minutes and that is what the disease look like? How do you find it? And that kind of stuff.

Dr. Cromwell: But clearly if you're that guy, then leaving you there is not good and you have to do something for it. All right. So then the second step in the process is the question of are there other issues metabolically going on that are causing your numbers to be bad in the first place? So there are a lot of secondary causes and people watching this know, hyperthyroidism, diabetes, liver problems, kidney problems, certain medications, diet, a lot of things can muck up your numbers. So before we go to a statin, we should do our due diligence. What's going on with the person? What are the different moving parts? If you break it down, if you're a splitter and you split things up in a small piece, there are 70 plus secondary and primary etiologies for a protein problems. What combination of 72 do you have? And that's a lot of what I do in my clinic. It's we sit down and do various things to try to unpack what somebody has going on.

Dr. Cromwell: Well, let's assume you have taken care of those things and now you're still left with somebody who has risks that's unacceptable if you leave them there. Their numbers are still not where they need to be, now we've defined a candidate for medical therapy. So I take that intro to say that I think skepticism is good and I think that we should be critical in our thinking and I think there's a certain amount of critical thinking that sometimes people look at the different opinions,

but I think the data should inform us and we should learn from data over time. And that's where we are. We're learning from data over time. All right. So will I start with a statin?

Robb: Just really quickly and you're painting a picture of a profoundly complex process, layer upon layer of different variables here. Yeah, yeah.

Dr. Cromwell: Right, exactly. So will I use a statin? Will I use something else? Will I use the PCSK9? Part of that answer is how much data do we have? Part of that answer is physiologically, what's the agent doing and how can it do its best job? So statin's been around since the late '80s. We've got millions of person years internationally. We have hundreds of clinical trials. We have a large repository of data. So one thing we can say is we know a lot about statins. We know a lot that's good, we know a lot that's limiting, we know a lot. And because of that, it's our go-to agent because of the quantity and quality of data that informs. So I think that's okay. And the guidelines say basically for that reason, statins are your first step, unless there's a reason not to. Now, what does statins do?

Dr. Cromwell: Well, just simplifying it, statins upregulate LDL receptors. LDL is a portable. It carries cholesterol. The particle is cleared from the body by binding to an LDL receptor, being pulled into a cell and being clear. The more LDL receptors you have, the more particles you bind and you clear. So that is the mechanism that LDL goes down by a statin. The steps that are involved are a little bit more intricate in that the cell has an enzyme, HMG-CoA reductase, which is the rate limiting step of cholesterol synthesis. Our cells are very explicitly tuned to maintain a constant or near constant homeostasis, and that's a long conversation. But if you decrease cholesterol synthesis in part by inhibiting that enzyme to maintain homeostasis, there's a compensatory response and the response is, "Make more LDL receptors." So that's what statins do.

Dr. Cromwell: PCSK9 inhibitors. PCSK9 is a protein that was discovered in the early 2000 timeframe as a protein that regulates how often an LDL receptor goes up, finds a particle, pulls it into the cell and repeats the processes. An LDL receptor on its own can do that several hundred times in a normal life cycle. So the normal life cycle of an LDL receptor is catching clear many, many, many times. Now, if that's true and you turn on a process to fix a problem, "I need more cholesterol on myself. I'm going to make more LDL receptors. What do I do now? I got to turn the machine off." If that receptor has a lifecycle that has hundreds of opportunities to do its job, it needs a regulator and the regulator is PCSK9. So PCSK9 basically says, "Here's the LDL receptor. I'm going to grab it, pull it down, and not let it go back up. I'm not going to let it recycle." So PCSK9 is a chaperone protein that limits how many times an LDL receptor can recycle. It's the way the body tunes the LDL receptor response so that it can stay tightly regulated.

Dr. Cromwell: So if we think about it, if you get rid of PCSK9, it's like taking the restrictor plate off of an engine. You're just going to let it run. It's going to run wide open. Some of the LDL receptors run wide open. So if I start with X number of receptors and they're running wide open, that's going to reduce LDL levels by a certain amount. What if I start with X plus an additional number of receptors? Then I have more receptors all running wide open. That's why if you put a PCSK9 on top of a statin, you get a better LDL reduction, just a PCSK9 by itself.

Robb: Got you.

Dr. Cromwell: The guidelines in part, because of the quantity and quality of statin literature is they start with the statin, and then because PCSK9s are significantly good at lowering LDL and work better in an environment where you already have more LDL receptors, the usual rules of the road are start with the statin, maybe add more oral therapy like ezetimibe or something else that you need, and then finish it off with the PCSK9 inhibitor and knock the socks off your LDL level. Now what happens when people can't take a statin? And there are a lot of statin intolerant patients out there. Can they take a PCSK9? Absolutely. And if they do well, they get a significant LDL reduction. They will. Will it statistically be as good as if they had a statin on board in the first place? Probably not. They probably do best if they had both on board, but if they only had a PCSK9 they do really well.

Robb: And Bill, is that due in part also that there are these layered effects? Statins also have an anti-inflammatory effect. They also have some stabilization of plaques. This is where we get so myopic just on the lipoproteins and cholesterol that these things do other things, sometimes beneficial, sometimes challenging, but is that part of what's going on there also that the statins in particular have a multitude of effects and that might be why you get greater benefit?

Dr. Cromwell: Yeah. That's well said. So pleiotropic effects is that basket of other good things that statins do that aren't related to LDL levels and they are important and there are many of them. The challenge we've had through the years is trying to figure out how much benefit we think comes from any one of those extra effects or that group of effects versus just LDL lowering. People have tried and I've not seen anybody agree as to what percentage of benefit may be attributable to these other things, but "prego" it's in there. Right? It's all good. It's all in there. And as you said, we want to affect the disease, and effecting the disease includes decreasing inflammation, decreasing plaque formation, improving plaque stability, decreasing plaque rupture, decreasing thrombus formation, all sorts of things other than just LDL lowering. As important as LDL lowering is, it's not the only thing and in many cases, it should be part of a much broader consideration of what's available to make things better.

Robb: Okay. That was a lot. And we're only one question in and we have 60 questions. This may end up being a four-part podcast here. Let's see here. How much are these results that Precision Health Report effected by recent behavior? If someone's been eating/living totally out of whack a week or two and takes a test, how much does it skew the results? Which results are most effected by recent behavior? So people are trying to figure out how to cram for the test or vice versa. So how stable are the markers that we are really concerned about within the Precision Health Reports? Can one week of bad eating really pushed that unfavorably in a poor direction?

Dr. Cromwell: So the question is how stable is their physiology, as well as how stable are the numbers and those are related to different things. And I know we're going to talk about lean mass, hyper responders, and some other interesting topics, and I think that Dave Feldman has probably helped more than any one person in giving visibility to how radically our bodies can change in just days. Right? So if you really throw the switch hard in one direction for days, you can really change the numbers. And you throw the switch hard in another direction for more days, you can mess things up in another way. So our physiology is amazing in that we can take a licking in many ways to keep on ticking, like the old Timex commercial, and that has to be the case. I mean, in free-living environments

where a meal is not promised to you and you're running down trying to catch some food, who knows what condition your body will be in one day to another?

Dr. Cromwell: You may be in a overfed state one day, in a fasting state another. You may be eating a lot of animal protein because that's what you could get one day and eating plants on another, and as a result, your diet can be all over the board. And what you're doing is you're having to in real time process and use in a non deleterious way all these various food sources and that's the way we'd been engineered. So back to cramming for the exam, you can actually influence these results quite a bit in a three to five day period of time, depending on how radically different you've changed things over that period of time. So the expectation is that you should be in your usual state before you get the test done for at least a week or more.

Dr. Cromwell: Before you get the tests done for at least a week or more, right? What we would prefer is that people make an adjustment that's sustainable. And you're in your sustained whatever state that you've adapted to or acquired and we test you and then the numbers teach us something. And then in response to the numbers and other variables and how you feel, you consider making another change and you make a change and then we want that change to be sustainable for several weeks. After a sustainable change for simple weeks, we can say, what is the body doing in this new set point that is now your new normal? That's the idea. Now the more radically we go away from a sustainable change to a, I got three days, let's make this happen. And you go on some kick for three days and you get numbers, that's just confused.

Dr. Cromwell: That's confusing. It's confusing because we expect the body to do things under those circumstances that are dynamic and real and different. And they very often don't reflect your usual day to day. That gets us to the concept of why is a risk factor a risk factor? It's a risk factor because it is a problem over time. Time is a critical variable for health and a critical variable for disease, and it's often not discussed. It's one of those things that unfortunately, I think we have a blind spot to in lipidology. We don't consider a time dependency of things. By that I mean, if you were trying to understand the relationship of smoking with lung disease, heart disease, whatever, you would ask, how much have you smoked and for how long? And that's just the way you look at it.

Dr. Cromwell: If you just picked up a pack of cigarettes yesterday, and that's your new habit you've acquired, I have no way of judging next year, how deleterious that is for your long-term health, because it is quantity over time, right? Well, the same thing is true of many other things that we're doing. How long have you been that way? And conversely, if you make an improvement, how long can you stay that way? It's really, think of it like compound interest. Money's good, putting it into someplace it's bearing interest and leaving it for a decade, is great. Compound interest takes over and you're a happy guy 30 years later. Take the same amount and bury it in five years, it's okay. But you didn't get the big payoff until much later on, right? We really need to think of, again, back to this regulated, dysregulated state of find people early, fix what's wrong.

Dr. Cromwell: Get two parameters that are likely to be beneficial and stay there for a long time. That's what defines success. And conversely, if I inherit somebody as a new patient, who's 40 years old and I have no concept of where they have been. They've not seen doctors regularly except when they're ill, their wife nagged them into the office, they got some tests for the first time and lo and behold

they look bad and the guy says, " What should I do?" My first question is, "Well, how long have you been that way? And what's wrong with you?" He said, "I have no idea."

Dr. Cromwell: If you have a bad LDL number, how bad is that? Well, what's the number? How high is it and how long has it been that way? That's the problem. So if you're a guy who has been unfortunately cursed with familial hypercholesterolemia, and you have high LDL from birth, and that's not taken care of until your thirties and forties, you're in trouble, you were in trouble at a stage long before that even. But if you have gone through a recent change, you've crammed for the exam and you've gone off the rails and numbers are stupid high, and you just jacked your LDL cholesterol over 350, I'm not saying that's bad. It's not problematic unless that's your new normal, you stay there for a long period of time. There's the rug. How much concern should we have? You should put it in context. And the context is everything.

Robb: I love it. Love it. Let's see here. This is a good one. What trends could we expect with dietary change? For example, when people switch from a standard American diet to paleo keto, sometimes their total cholesterol goes up. What changes like these can we anticipate so that we can proactively address them? I have my thought on this, but I'm super interested to hear your thoughts on it.

Dr. Cromwell: Well, again, I think context is important to answering the question. Are we talking about an insulin sensitive person? Are we talking about an insulin resistant person? What does the standard diet look like to begin with? And what is your application of paleo keto principles? These are all moving parts. And so it influences my answer. I've seen people with the standard American diet, which is variations of bad, and it looks like a lot of processed food, a lot of a junk food, a lot of refined food, very little food in its natural state, very imbalanced in its macro nutrient distribution.

Dr. Cromwell: That's one way of starting. Now, if you adapt or you can transition to a different diet, you can have a diet which is a paleo diet, which emphasizes foods in their natural state and then the processed, a good variety of healthy carbs, healthy fats, etc., that's one application principle. You can add to that an application principle that says, well, I really am concerned about carbs, so I'm going to cap carb in addition to that. I'm going to not exceed a certain amount of carbs and I am going to try to emphasize the better quality carbs.

Dr. Cromwell: You can take that a step further and say, well, now I'm going to put a more severe carb cap on it to instill ketosis. Now it must be 50 or less than 20, whatever that number is so that you can get to a ketonic state. All right. And then as I'm doing that, what are the macronutrients that are taking up the burden that aren't being satisfied by carb capping. Right now I'm taking in more fats. What kind of fats are you taking in? Are you taking in a blend of polys and monos and saturated fats? Is there any attention to detail as to how much saturated fat or are you going out of your way to add saturated fat? There are some people who would do that. Unfortunately, all of those things have their own nuances and impact on what you should expect to see. That's just a statement in general. Now apply those statements to a normal individual's insulin sensitive tissues, an individual who's insulin resistant and on their way toward the insulin resistance syndrome, individuals who have full blown insulin resistance, and then all the way to diabetes.

Dr. Cromwell: You have four different types of individuals reacting to a myriad of individual applications of principle. And what I'm going to tell you is in my experience and data I've seen is there's a wide range, we're buffered. We're buffered to accommodate a lot in general, as we adapt and move toward a paleo or keto type of diet in the insulin resistant individual, you'll see the greatest amount of change. And in the insulin sensitive person you'll see change, but not as much. Those are just general statements. The change that you will typically see is a reduction in triglyceride, an improvement in particle number, an improvement in HDL levels, an improvement in insulin sensitivity. And there will not be a sharp increase in cardiovascular risk as you're transitioning to a higher fat diet, there are populations that eat a high fat diet on regular basis and do okay with it.

Dr. Cromwell: But there is going to be a point at which, and it may be highly individual as well, you cross a threshold where you are now going to be in a difficult spot trying to maintain normal physiology because you have gone over the edge for total fat, you've gone over the edge for saturated fat. One of the things that we know in this extreme example is you down-regulate LDL receptors. And when you down-regulate LDL receptors, you are not going to clear LDL part of this. This then gets into, I think, a very interesting conversation where there are a lot of theories and they all have merit. I can't say anyone is right or wrong, but I think the complexity, as you said before, is the challenge. We have all these complex things that are interacting in the short-term in the long-term.

Dr. Cromwell: In Dave Feldman's energy model, he would say that, we're taking all those fat in and we're going to be trafficking it to cells for the right reasons. And that's going to potentially cause us to make more VLDL and cause us to potentially make more LDL. And now these particles have to be cleared under the circumstances they are normally clear. Well, that's a relative state.

Dr. Cromwell: At what point does it show up as a crazy high portable number? That's the extreme, and that's not going to be for a while. Relative changes are relatively small and big changes happen at the extremes of as I tell my patients, cars drive well on roads and poorly in ditches. There's a high-fat ditch, there's a high carb ditch. Don't go in the ditch. And there's a big road in between. That big road is what I'm describing with paleo or keto, a variety of applications of principle that get away from the standard American diet to a diet which is better in any number of ways, but can breathe if you will, right? It's not so tightly tuned that if you exceed 50% calories from fat, you're doomed, not necessarily true. If you exceed 50% calories from saturated fat, you're doomed, not necessarily true. As a result, that we can accommodate a lot, but after a certain point, you will get into an issue.

Dr. Cromwell: And the issue that I am most concerned about is not what happens in the short term. I'm concerned about what happens as your new normal over years. That's the problem. And so when I watch interesting conversations about how dynamic our body is tuned and how much we can change in a short period of time, I always want to bring back the conversation to that's great, but are we talking about long-term change or short-term change? If now you're telling me I have a really high LDL and I'm going to be that way for a long time in phenomena, I don't change anything. That's a different conversation.

Robb: Right. Bill, really quickly in that scenario. What is the mechanism that would down regulate the LDL receptor sites? Is it the intake of saturated fat beyond a

certain level or what typically is going on there? I could think of several things, like potentially thyroid downregulation or host to different vectors on that. But what do you think is really going on there?

Dr. Cromwell: Yeah. Well, the study has been done in a variety of tissues, animal models to humans, so there are different points of view for that. One of the things is that when you are delivering sterols, fatty acids, etc., in large bulk to tissues, you are going to affect in a feedback's signaling mechanism, what the cell is seeking to do. The cell in real time senses and responds to changes. One of the changes is that by changing our diet and changing our fatty acid composition from cooked food, saturated fat, and whatnot, this shows up in cell membranes.

Dr. Cromwell: Cell membranes are a huge repository in our body for cholesterol and in a very dynamic and very changing environment in respect to what our diets are with proof or with saturated fat or whatnot. If you think of the cell as the beginning of the conversation, that the cell tunes its cholesterol levels in such a way that it's reacting to what's in the cell membrane, it's reacting to the amount which is being synthesized by the endoplasmic reticulum and the transfer of bulk cholesterol, if you will, between the cell membrane and the ER, endoplasmic reticulum. Those levels in real time through nuclear receptors and sensing organisms in the cell, turn on and turn off synthesis and LDL receptor recruitment of LDL particles.

Dr. Cromwell: We're doing this in real time, on a minute by minute basis. And as a result, there's always this little bit of adjustment going back and forth. Now what happens when you make that a different type of homeostasis? Right now we are just delivering, delivering, delivering, delivering free fatty acids, delivering sterols. Now the cells are inundated with this. One of the mechanisms that is available is trained off LDL receptors, down regulate LDL receptors. We don't need to bring cholesterol into this environment. We're handling a lot as it is. And some of the cholesterol that's on the surface is going to be taken out by HDL particles and reverse cholesterol transports. We're going to be getting rid of it that way. In the liver we're going to be shunting toward bile acid synthesis and other ways to get rid of it into our gut.

Dr. Cromwell: We're doing all sorts of things in real time to try to keep things within certain parameters. Once we exceed that and we have this net excess of fatty acids and sterols, it's going to result in shutting down some processes more than usual, down regulate LDL receptors, as well as bulk movement in other areas. Again, this I think that the question of what do we do within certain limits on a normal basis? And then when we are way off into a new sphere that the cell can't easily accommodate, it's going to have to make some more long lasting changes like down regulate LDL receptors.

Robb: That's-

Dr. Cromwell: Another example of this which is interesting is the other extreme, and that is anorexia nervosa. A good board exam question is, you've got somebody with anorexia, what's their LDL level? It's super high. Why is it super high? They can't make LDL receptors. LDL receptors are a very energy intensive process for the body to undertake. And if you are trying to shut your mega calories to critical body functions, that's one of the things that doesn't get a lot of attention to detail because I just don't have energy for that. But it's correctable. I mean if you correct their energy deficits, they will go back to making a more reasonable

number of LDL receptors. And similarly, if you're that person who has taken on a very high fat diet with an aberrant and persistent high LDL response, then you can back off your fat intake and you will largely dampen that effect.

Robb: Bill, that gets me thinking, could some of the problems that we see let's say over the timescale of a month, people are isocaloric, but they're introducing these really extended periods of fasting. They may go 24 hours here or 32 hours there, could they transiently be causing that energy deficit problem so that this may be a pushing LDL particle up because the body is sparing the production of the LDL receptor because of that energy deficit transiently and that could actually be feeding into these elevated lipoproteins long-term?

Dr. Cromwell: I think the timeframe would have to be much longer.

Robb: Okay.

Dr. Cromwell: I think we haven't done really great experiments to find that out yet, but connecting the dots that are available would be only over months or a week rather than days. Again, because if you think about how we're just engineer, there are a lot of hunter gatherer societies where people fast for extended periods because they just don't have food. And they're still able to maintain normal cellular homeostasis with cholesterol. They still have to have LDL receptors to be part of that process. So it's a very late thing to fall off because it is an integral part of homeostasis. But it's energy intensive and in large energy deficits for extended periods of time, it takes a hit.

Robb: Okay. It's still that chronic versus acute story. Yeah. Okay.

Dr. Cromwell: Yeah.

Robb: And now a quick word from today's sponsor.

Nicki: This Salty Talk episode of the Healthy Rebellion Radio is sponsored by Element, our salty AF electrolyte company that hydrates you with all the salty goodness and none of the sugar found in typical electrolyte drinks. I wanted to read a review from one of our element customers, Jen. She says, "Holy cats, this is good." Whenever I see holy cats, I know that the-

Robb: Old school.

Nicki: The person is old school and has been following Robb for some amount of time. She said, "Wow, who would have thought salt could taste this dang good. I've tried every flavor offered and there isn't a bad one in the bunch. I started taking element because I'd been noticing I was frequently getting light-headed when going from relaxed to standing and I thought it could be an electrolyte issue leading to a blood pressure issue. I've been supplementing with a half a packet to a whole packet a day, depending on activity and sweat levels for the day, for the past month and I haven't had any lightheadedness since starting.

Nicki: I'm actually shocked now at how much it has been affecting me. It's every time I stand up, I find myself preparing for the walls to close in, but they don't. I know this may seem like a silly thing to be excited about, but if that was the outward symptom I was having due to insufficient electrolytes, I can only imagine all the other little things that weren't firing on all cylinders inside of me that I don't see

or feel. Thanks Element for making a quality product with quality ingredients that taste good. Stay salty folks."

Nicki: That was a pretty cool review. Our new limited time flavor, grapefruit salt continues to impress and be popular. Get your hands on one of those before they are gone. You can also build a value bundle of your four favorite Element flavors. And with the value bundle, you get... When you buy three boxes, you get the fourth box free. Just go to drinklmnt.com/robb, that's drink, L-M-N-T.com/R-O-B-B. And now back to today's episode with Dr. Bill Cromwell.

Robb: This is a good one and very practical. What's the best way to share precision health reports with one's doctor? I sometimes have to cover my eyes. We empower folks to go through a process like this. They get super well-informed. They go to their primary doctor and the doctor's like, "I have no idea what this stuff is. What is an LDL particle number?" And they just kind of, everybody throws their hands up in frustration. I think is the bigger picture there. But where have you seen success with this? If the doctor is educated and open to this, it's probably a pretty easy story, but we're still probably talking 99% of primary care docs aren't really well-versed in this stuff.

Dr. Cromwell: Precision health reports has moved from what's your particle number to integrating guidelines in a way that doctors are much more comfortable. I think that's one answer is that when exposed to the information in the precision health report cardio metabolic risk assessment, it bears a lot of resemblance to things people know about. It adds a layer of detail about the individual, but it's not starting from the standpoint let me teach you something new. It's starting from the standpoint of cardio metabolic risk is a jigsaw puzzle with over 40 interconnected pieces.

Dr. Cromwell: The doc knows a lot of these interconnected pieces, but the challenge is the history, the physical exam, the laboratory test, the guidelines that put these 40 pieces together are beyond the day-to-day practice of the average physician. Add to that the complexity, the guidelines for the past five years have taken a hard step toward trying to incorporate important clinical elements that further accentuate risks that aren't part of the traditional pathway.

Dr. Cromwell: We call these risk enhancing factors. There are over 30 risk enhancing factors the guidelines say clinicians should consider. What do they include? Well in women, for example, are you experiencing menopause before the age of 40? Are you pre-eclamptic? Inflammatory disease, do you have psoriasis, rheumatoid arthritis, HIV? The list goes on and who knew that all of these things are significantly associated with individual risk being increased beyond the traditional pale. All of these things are out there. They're all part of the guidelines. But if you ask a doc, let me just give you an example.

Dr. Cromwell: I had a 42-year-old guy who came to see me. He came from Texas, relocated in North Carolina, and the reason he came to see me was he said, "My mom was diabetic and my dad had his first heart attack in his fifties. What about me?" He's 42 years old. I say, "Well, what do you know about yourself so far?" He says, "I know I don't take any medicines. I don't have any chronic medical problems. I've had a couple of labs done recently and the only thing that I was told watch out for was my good cholesterol was down a little bit. My triglyceride was up a little bit and my blood pressure was borderline." Okay, so that's our starting point. I ran a cardio-metabolic risk assessment and so what were we

interested in? We were interested in all of the historical factors that would give us visibility to those risk enhancing factors. We looked at an NMR LipoProfile test. I had his lipids. I had his particle number.

Dr. Cromwell: I had his lipoprotein insulin resistance score, LPRS score and a Glyc A. I also had LP(a), and I had fasting glucose. Now those tests together are all the information I need to take first steps with this individual. Here's what I found. His systolic blood pressure was 134, a little bit up; his diastolic blood pressure was 88, a little bit up. HDL cholesterol, 34, a little bit down; triglyceride, 170, a little bit up; fasting glucose, 102, a little bit up. If you are a savvy doc, you would say, " We only have more than three features of the metabolic syndrome. I think that you're a metabolic syndrome patient." Okay, well, let's break that down for a second.

Dr. Cromwell: You've given me categories of numbers and you get a check mark you're either good or you're bad. Does that mean that everybody with the same number of check marks has the same metabolic syndrome related risk for diabetes, heart attack or stroke? The answer is no. The limit of that statement was actually shown by a guy named Mark Burr and other researchers from University of Virginia and University of Florida, who came up with an amazing tool called the Metabolic Syndrome Severity Score. What that score does is it takes your actual numbers for waist circumference, blood pressure, blood sugar, HDL, cholesterol and triglyceride, and puts it in a multi marker that's weighted.

Dr. Cromwell: It's been tuned to different ethnicities, gender in large outcomes studies like ERIC or large populations study like ERIC and others. And what it tells you is on a one to a 100 scale, where are you with the severity of your metabolic or insulin resistance syndrome? A higher number is higher risk for diabetes, heart attack, and stroke, and a lower number is less risk. Now I'm taking you from how many checks do you have to a continuous risk of how bad are you.

Dr. Cromwell: I've seen people with two of the metabolic syndrome factors present. The other three didn't get a check, but they weren't far off and their metabolic syndrome severity score was very unfavorable. I've seen people with three checks, just barely out of range and the other two are perfect and a much lower metabolic syndrome severity score. What we need is a way to unpack this insulin resistance, right? And so when you're looking at the report it's saying, okay, I have insulin resistance as identified by lipoprotein insulin resistance score one to a hundred. It tells me how insulin resistant or how insulin resistant I am. I've got metabolic syndrome severity score one to a hundred. How bad am I? How good am I?

Dr. Cromwell: Now you see, we're adding a better visibility to the individual *[audio cut out]* you know about. What about diabetic risk? This guy had a glucose of 102, that's barely out of the normal range if you consider 100 normal. But he had an LPIR score, a lipoprotein insulin resistance score of 85, way high. His eight-year risk for diabetes was 35%. Very high. But that's a 102 of glucose. And what does that unpack for us?

Dr. Cromwell: We know from MESA and other large studies that men and women behave slightly differently, but the higher the glucose, the greater the potential risk for diabetes. That's what ADA tells you. But now let's just pick a number 110 as an example. At a 110 glucose, what is your actual range of diabetic risk? It may range from 15% to 45% or it's just an example. There is a wide range of actual

risk at a given glucose study. Knowing that, what the ADA said several years ago is we need a better approach to discriminate individual risk at any glucose level. And that's what we do, taking advantage of MESA data, Proven, CARDIA data. We are able to integrate fasting glucose, insulin resistance score by gender and give a specific eight-year diabetic risk, which is highly responsive to diet, exercise, improvement in sensitivity and improvement in glucose.

Dr. Cromwell: That's another part of the report. Now the doc is saying, "I know about metabolic syndrome and this teaches me more. I know about insulin resistance and this teaches me more. I know about diabetes and glucose; this teaches me more. What about cardiovascular risk?" Well, let's do the calculator. Because everybody says, do the calculator. I do the pooled cohort equation. I got a 10-year risk. I got a lifetime risk and that's a number. And it says based on a population of individuals, I have a percent chance of having a heart attack or stroke in a given timeframe. What about these risks enhancing factors?

Dr. Cromwell: By virtue of the data that we take in we're able to identify all 30 plus risk enhancing factors, put them into the equation as well and come up with an overall risk, which is highly responsive to the individual, their gender, their ethnicity, etc. And now it's like leaving no man on the battlefield, right? We're not going to leave anybody behind, everybody's accounted for. And therefore, we're not looking at these numbers and saying, I wonder what I'm missing. I'm integrating all of this information so that in a single report, you can see what's there.

Dr. Cromwell: Some of it's modifiable, some of it's not. But that which is modifiable, we can not only modify it, but we can track your response over time. And that gets back to it's what you improve and how long you improve just a real calculus for benefits. The advantage of precision health reports is that I think we're bringing to the clinician the opportunity to not have the challenge of it takes me 20, 30 minutes to do all of this one patient at a time. All I have to do is type in the name and email address and the next thing the doc sees is the report. And the report is laid out in a way that it builds on what he already knows. It fills in the gaps of what the individual has going on that you wouldn't otherwise necessarily know. And it gives you a better way to have the informed conversation, one patient at a time, what can we do about this?

Robb: Fascinating. It's-

Dr. Cromwell: So...

Robb: …incredible and-

Dr. Cromwell: Back to your question-

Robb: Yeah.

Dr. Cromwell: Yeah. How do we get that information to the doc? Well, the patient can give it to the doc, but like we said, the doc will say, “Wow, this was really cool, but I'm not sure." Right. There are health coaches that were empowering and health coaches are conduits of change. They're the change agents. They are the people who go out there and help people understand and give them options of what are you ready to do. Are you ready to make a dietary change? Are you ready to

make a smoking succession change? Are you ready to take on exercise? What do you know about these symptoms? Right.

Dr. Cromwell: They can facilitate change. I'm available. I take a lot of calls from both patients and docs. "I got this cool thing. What does it mean?" And as we gain awareness and as more and more people are supposed to begin to use this tool, I think it's going to be something that it's going to be very valuable and it doesn't have the limitations for example, that we've seen in past where I bring you a new laboratory test, you're unfamiliar with the new laboratory tests, but I think it's the greatest thing since sliced bread. And I'm giving it to you and I want you to just immediately incorporate it into your practice. Maybe that happens, maybe that doesn't. Maybe a better way is to say, we all are trying to do the same thing, the right thing for one patient at a time and this is a tool that gives you the visibility.

Robb: Amazing. Yeah, I think that is so smart. And clearly this has been a very long process of refinement. And it's just amazing to see how this... And it's going and it's great because I've always found myself to be in that educator role. It's like here's CrossFit or paleo or whatever the thing is. And even if the theory is sound and it will be born out over time, it sucks to be in that trendsetter role, because you've got to do the education process and everything. But if you can, it's like hiding the broccoli in there. If you provide a report that the doctor sees MESA and they see nurse's health study and they see all these things they are familiar with, they're like, okay, this isn't too freaky. There's a little bit of lab diagnostics...

Robb: They're like, "Okay, this isn't too freaky. There's a little bit of lab diagnostic stuff I may not be too comfortable with, but here's a very clear delineation of what the risk profile is from a diabetes perspective, a cardiovascular disease perspective." I could see where that would put the physician at ease instead of prickling the hairs on their neck. And they're like, "What the hell is this?" And you have highly trained people, they don't want to look like a dummy either. So, the patient shows up and they know more about a test than the doctor does? Then you're in this like, dick measuring contest immediately over that, you know? Which is never good.

Robb: So, I really like this. It makes a lot of sense that this would help facilitate just information transfer and then setting the physician up to say, "Yeah, I like the direction you're going with these diet and lifestyle changes." And to your point again, we're going to track this over time, see where it goes. If it goes favorably, great. If it doesn't, then we need to adjust what we're doing and there we go. Yeah, awesome. Let's see here...

Dr. Cromwell: The other thing I'll tell you is, resources. We're developing a tool kit, if you will. I mean, if you go to our website, there's certain content that's available. There'll be more content over time, both in basically a written form or verbal form or video form. I think a podcast like this is critically important to help people understand what's out there and get the word out, so to speak. We all learn differently. Some are visual learners, some are auditory learners. And so we just want to surround this report with tools that would give people understanding, visibility, their provider, their healthcare team. I think we're in a day now where people are getting to be more empowered, people are taking more ownership of their wellness. People are wanting to be advocates for their wellness. And I think this is a good thing.

Dr. Cromwell: It's no longer the time where if I want to know something about myself, I have to go to my doctor and hope that he has time for me. It's, my doc's a critical part of my healthcare team, but my team is a team and he's part of it. And I'm responsible for my own health. And I need to do some things to understand where I'm at, see how I'm doing, when I make the changes.

Robb: Right, right. Yeah, it's awesome. I'm glad you mentioned that because you guys are, and we are... Some of our health coaches and then just what we're learning from people going through this within the Healthy Rebellion community is really helping to inform where folks have questions. And you guys are working like monsters to generate materials so that folks can have that easily accessible information, whether it's a downloadable PDF or a short video segment, or what have you, so that people can get in and continue to customize their experience on this.

Robb: You ready to jump into what do you think of lean mass hyper responders? Like that's liable to be a... Could be, depending on... I'm trying to play Carnac the Magnificent and predict your future deal here. I could see this being either very short or very, very long. So, what's your thought on that?

Robb: And maybe for some context, most folks within our community are familiar with Dave's thoughts around this lean mass hyper responder. And he has put forward this idea that this is a energy transfer up-regulation process because you become very fat centric in your fueling. The problem that I've had with this is when I've done a little back of the envelope calculations of how much energy is getting shoveled around in lipoproteins relative to triglycerides, I don't see how that's a really significant contributor there. And I asked Dave about that. I'm like, "Hey, have you ever sat down and just done the stoichiometry of how much energy, how many kcals of energy are locked up in all of these classic lipoproteins relative to just the triglyceride fraction?" He's like, "No." Well, that seems like an important thing to do. And again, I've just done some back of the envelope stuff, because there's a lot of variables there, but it seems like an order of magnitude or two different between lipoproteins and triglycerides. So, I find challenge with this notion that it's just an energetics story, but what's your thought on that?

Dr. Cromwell: So, that's part of my observation as well. Just taking several steps back, we are certainly able to accommodate a variety of changes, but at the end of the day, cells need energy and that energy comes from somewhere. And if we just start with the gut, we have to take a food, break it down, package it and get it into the body. And that's done primarily through chylomicrons. So, chylomicrons take sterols and free fatty acids, and as it enters the circulation, it has a relatively short timeframe. Within hours, chylomicrons are gone.

Dr. Cromwell: And what's happening? They're going to tissues, lipoprotein lipase are hydrolyzing and releasing triacylglycerol into muscle and adipose tissue in places that need energy. And so, the first step of the process is we are supplying a lot of energy from chylomicrons directly to tissues via this type of pathway.

Dr. Cromwell: It also goes to the liver and the liver is a master at integration. And it's integrating that along with other things that it has access to and it's repackaging into VLDL and sending it out, that's happening as well. But at the end of the day, a lot of the energy that we are going to be using from our diet is going to be shuttling through chylomicrons, lipolysis into cells before we get to the VLDL

absence. And that's part of the challenge of trying to account for where is all the energy going and where are the cells getting the energy they need? That's a lot of it. And I think that takes a good bit of the back of the envelope calculation and begins to square it, because there's not as much conversation about energy delivered through chylomicrons, as energy delivered potentially through VLDL, right?

Dr. Cromwell: So VLDL particles actually are a way to offload fat from the liver, if you want to put it that way. So the liver, as it synthesizes fat, has one of three things it does with it. You package it up into VLDL and send it on its way. You oxidize it, beta-oxidation. Or it sits there and you get steatosis fatty liver. And those are the big three things that the liver does. So, not wanting to be steatotic is a good thing. And the liver is programmed to not be steatotic. If I have any chance, I'll either burn it which is slow and sluggish, or I'm going to mate it with an APO-B through MTP, and I'm going to make a VLDL particle and send it on its way. But that is a multi-step, timely process. It is a rate limiting process. You cannot offload off all the fat by just up-regulating VLDL.

Dr. Cromwell: VLDL can only up-regulate to a certain degree, and that's why you have steatosis because you just cannot keep up with as much substrate as there is to be packaged and exported. So, that's another limitation of the system, right?

Dr. Cromwell: So, VLDL then is also going to be hydrolyzed. It's also going to give up this triglyceride. It's also going to be fueling things, it's going to be forming LDL and LDL has a much longer residence time in blood than it does either chylomicron, chylomicron remnants, or VLDL or VLDL remnants. So as a result, LDL on the order of days, three days, good round number, right?

Dr. Cromwell: So, you've got these as the major moving parts for lipoprotein metabolism and energy handling, if you will. So I do think that a lean mass hyper responder is using energy differently than say, an insulin resistant individual. An insulin resistant individual has a lot of this energy being packed into adipocytes. And lean mass hyper responders, a lot of these... A lot of this energy being used by muscle, and much less being packed into the lipocytes, fat tissue. So that's one difference.

Dr. Cromwell: Another difference is the fact that lean mass hyper responders are insulin sensitive, and therefore they don't have a lot of egress of free fatty acids from their fat cells, just as background. Whereas an insulin resistant person has trouble holding onto the fat in their fat cells. They leach out free fatty acids on a regular basis. It goes into the portal circulation, it hits the liver. The liver says, "Oh, I can use this to make a triglyceride," makes triglyceride. Now I have to do something with the fats I've made, make more VLDL. Large VLDL particles that are fat enriched are sent out of the liver, that gets degraded into LDL. And so, part of the problem here is I've got all this background substrate, that's hitting the liver, making more VLDL in the insulin resistant person. In the insulin sensitive person, that process is dampened to very little.

Dr. Cromwell: And so, that's a fundamental difference between a lean and a insulin resistant individual, right? So just physiologically, they're different and they're processing metabolically labile proteins differently. Now add to that what energy substrate you're giving them. So, the lean mass individual can either be a lean mass guy on a paleo diet, a Mediterranean diet, or it could be a keto diet with a lot of fat. And you don't have to be only a keto diet person to be a lean mass person,

right? So you take those two things and wed them together and you get to a situation in a subset of a subset of people. So you have lean mass people, you have lean mass hyper responders, right? Or as Dave would say, you have hyper responders and then you have lean mass hyper responders. So, you have a subset of a subset.

Dr. Cromwell: And that subset of a subset are an interesting group of people who, for reasons that are very complicated and probably all of the above, have multiple reasons to have a disordered LDL response to a high-fat diet. And their disordered response is a persistent elevation of LDL. Now an elevation of LDL can be transient. And if it's transient and it's part of adapting and changing to a new normal, that's one thing. And we do see individuals who, on a high fat diet, spike their LDL up for a while. And then it begins to come back down to their more baseline level. That's not what I call a lean mass hyper responder, that's a transient adaptive response. But a lean mass hyper responder who has a persistently new high LDL, it's going to be that way, unless something changes. That's different. And I think part of that is downregulation of LDL receptors, right?

Dr. Cromwell: And so, we have just saturated the tissues with sterols and free fatty acids to the point that they need to dampen the system. We need to not keep importing LDL because that is counterproductive to my needs. My needs are already super... They're already, if anything, I'm trying to recirculate this stuff some other way through HDL, et cetera. Right?

Dr. Cromwell: So, I do think LDL downregulation is part of it. Could it be both? Could you have an energy balance issue and an LDL regulatory issue? Sure. I mean, it can be a very exquisite, integrated... I don't think it's one or the other, I think it's a combination of both. But to be persistent, I do think you're going to have to incorporate LDL receptor function into the equation, or it doesn't make sense.

Robb: And even woven into that, just a skosh of subclinical hypothyroid would precipitate all that too, because of the action of the thyroid on LDL. Okay, okay.

Dr. Cromwell: What's interesting about hypothyroidism is back in the day, way back in the seventies, people were at first surprised and then not surprised, that if you take a random cohort of high cholesterol patients and screen them, 10% were hypothyroid. In just a random population, that's a pretty high frequency of something that's a secondary etiology for hypercholesterolemia.

Robb: And correct me if I'm wrong, but pre-statin era, even folks with relatively normal thyroid values were put on some amount of thyroid in an attempt to bring down cholesterol levels, which didn't work out all that way.

Dr. Cromwell: Yeah, the Coronary Drug Project, that was one of two arms that quickly got stopped. Thyroid for everybody was a bad idea. Estrogen for everybody was a bad idea, too. Thyroid for everybody didn't make it. But then there were drugs that were under development called thymomimetics. They mimicked the LDL action or the lack of protein action of thyroid, without having a thyroid stimulatory function. So they were trying to kind of split the load very finely here. I want some of this, but I don't want some of that. And they never quite made it to market.

Robb: Interesting, interesting. Let's see here. How big of a risk is high particle number by itself when all other markers are good? And what's the best way to reduce particle number? A good friend of ours in the Rebellion, Kristin. She's interesting. And she's gone through a process.

Robb: So, she was originally running at an LDLP about... In the mid three thousands. She actually went on some hormone replacement therapy and over the course of time, that's down around 1,600 now. And she has had serial coronary calcium scans, and they're all coming back at zero. But she's still technically... She's definitely gone from very high to kind of, to your point, I think, on the borderline high level. Looking at the coronary calcium score, so far looks pretty good on that, but I guess the things to look at there, how big of a factor is the particle count, independent of everything else? And I guess that that's super hard to say because it is all a system and all networked together, but then what is... Maybe the three top things to do to modify a particle count number?

Dr. Cromwell: All right. So, this is another one of those probably not short answers.

Robb: Right, right.

Dr. Cromwell: But I'm going to go back to a concept we talked about a few minutes ago and that is chronicity. How long have things been there? There's a great article. It has stirred a lot of conversation, it's from the European Atherosclerosis Society. And it is from an international, very august body of cardiologists, lipidologists, leaders in this field, handling the data in aggregate, trying to understand; is LDL causally related to atherosclerosis? And at the end of the day, the answer is yes, it meets every criteria for causal risk factor. But the most important thing to your question is, what is the time dependent association of high particle number with disease?

Dr. Cromwell: And there are three points of reference that you can have for that question. One point of reference is clinical trials. Right? Now, clinical trials are designed to answer a question in a relatively short period of time, average about five years. And over a five-year window of time, if I take a high number and I drop it, there's relative risk reduction. Okay, then another is observational data, where we have populations on average 12 to 15 years. And now I'm falling for a longer period of time. What happens natively to people who have a certain LDL concentration? Is that problematic?

Dr. Cromwell: And then the third and the more recent one that people may be familiar with is Mendelian randomization. In Mendelian randomization, you assume that G aberrations occur with random frequency in the population, and therefore you let that be its own experiment. And when you do it that way, you can also better accommodate confounder variable effects. Because as you said, it is an integrative system. How can you adjust for confounders that are part of the same disease process as LDL? And how can you be very confident that LDL is uniquely doing something different than anything else when it's confounded by the mix of things that it's a part of?

Dr. Cromwell: And that's a very legitimate criticism, and it's something that's hard to overcome when you're looking at populations as they live and breathe and try to pick apart the contribution to risk of one thing like LDL. Well, when Mendelian randomization minimizes that limitation by saying, I have genes that are associated with very low lifelong LDL, I have genes that are associated very high

lifetime LDL, and I can select out genes that have known a confounding association, so that I'm only looking at a fairly pure population. And what you find is a strikingly linear relationship between LDL and risk as a function of time. So, the longer you have something, the more it's going to be a risk. So on the one hand, we have things like hyperbetalipoproteinemia, PCSK9 deficiency, genetic situations where you have chronically low LDL for a lifetime. And you can compare that to such things as LDL receptor defects and familial hypercholesterolemia, where you have high LDL for a lifetime.

Dr. Cromwell: And by knowing the human genome, you can segregate out confounder genes, so that you're looking at a more purified question. And the answer is, it is a strikingly linear relationship across any number of snips that do any number of things to LDL levels. So just, from the experiment of nature standpoint, is there a problem with having a high particle number? Over time, the answer is yes. But again, it's how much over how long now. Now, if you give me somebody who has a particle number of 3,000. First thing I want to know is why is it that way? And how has it been there? If I can't tell, then one of the ways I can try to infer that, is look for the presence of subclinical disease. This is where coronary artery calcium scoring or other non-invasive modalities come into play to determine, do you have atherosclerosis? And is it inappropriate for your age?

Dr. Cromwell: Now, coronary calcium is an interesting tool. It has strengths, it has weaknesses, like every tool has. One of the weaknesses, in my opinion, is it only finds one kind of plaque, a calcified plaque. So if you have a calcified plaque, it lights up and if you don't, it's undetectable. So what do you make of a zero coronary calcium? Well, how old is the individual? If we're talking about a 45 year old female, in MESA, zero gets you up to about the 88th percentile. So, zero can not discriminate individuals who are above the 75th percentile or not. It can't discriminate people who do or don't have subclinical disease.

Dr. Cromwell: Now, a positive number will. If you're a 45 year old Caucasian female with a number that is point something, you're already above the 88th percentile. You can very quickly get into the 90th percentile. So, the fact that somebody has a zero coronary calcium at a young age, is hard to interpret. What I can say though, is a plaque can show up in an uncalcified state at a young age, as a function of any number of pathophysiologies, including high LDL. And we can find that by, for example, B-mode ultrasound. If you use B-mode ultrasound, not duplex scanning, not trying to get the idea of, do I have a flow limitation one side or another, but what is the actual thickness of an area in the wall of the artery that I'm concerned about? And with B-mode, if you take your time and you have a skilled operator, you will go through the common, the bulb, and the internal carotid artery. And as you're going through this area, you're looking longitudinally, and you're looking cross sectional. And as you longitudinally and cross sectionally, you're going to find areas that may be focally thick.

Dr. Cromwell: Now, I see an area that's focally thick. This is a three dimensional image, or a three dimensional structure, then I'm viewing with a two dimensional technology,

Robb: Right.

Dr. Cromwell: So, the two dimensional technology, I have to pass over the area, both longitudinally and cross sectionally. As I pass over the area, it will grow and shrink. And as it grows and shrinks, I can... "Okay, stop." Find the area which is

maximal. And then, longitudinally. Grow and shrink, stop. Find the maximal area. And then, you can compare in multiple planes of image acquisition, what's the thickness? And if multiple planes of image acquisition, I find an area that exceeds 1.5 millimeters by definition, it's a plaque. 1.5 to 2.5 is on the smaller side, 2.5 to 3.5 is moderate. Over 3.5 is large. And so, finding plaque in the carotids is evidence of atherosclerosis. It is evidence of disease.

Dr. Cromwell: You should not have disease at a young age. It's very atypical, to find plaques in young people. It is not uncommon to find plaques in old people. So, let's put some numbers there. 80 and higher, about everybody has a plaque. There are exceptions, but I'm not shocked. Under 40, not too many people have a plaque, unless you have something else going on. In between 40 and 80, you got to move from A to B somehow, right? So, in younger individuals, B-mode ultrasound, finding the presence of carotid plaque is a very helpful tool for answering the question; has the process turned on, that I'm worried about being associated with high particle number? Right? So, in my hands, that's what I do. I actually image patients myself with B-mode ultrasound, takes about a half an hour to interrogate both sides of the neck. I read the studies with the patient, and I'm able to show them in real time, "This is your plaque. These are your plaques."

Dr. Cromwell: And if you have multiple plaques, similar in size, similar location, both sides of the neck, you've caught the body in the process, the hands are in the cookie jar, right? They got a zero coronary calcium. You don't have old calcified plaque yet, but you have the process that I'm worried about. And since LDL is a punitive causal risk factor, it does not need anything else to stimulate atherosclerosis plaque heart attack, over time, other than just time. It needs a sufficient amount over a sufficient time in order to have its negative effect.

Robb: And you mentioned a study that decoupled insulin resistance from LDL count, and because there is kind of a meme within low carb land that so long as your insulin levels are low, you're okay. You get the get out of jail free card for cardiovascular disease. And you said no, unfortunately it's not that easy. And could you remind me of which study? Or perhaps you've even alluded to that, but it decoupled the insulin resistance piece of cardiovascular disease risk from that lipoprotein part,

Dr. Cromwell: Well, so the Mendelian randomization studies have done that by using genes that have the ability to identify insulin resistance, as well as particle number. But more directly, I will tell you that we took a shot at this in MESA. And so, from the standpoint of having an LPIR score as an indicator of insulin resistance. LPIR score is significantly associated with cardiovascular risk, that has been shown in a number of populations and was recently published in the Women's Health study as well. So, that is one window into the insulin resistance state.

Dr. Cromwell: So, let's take an exercise, we have MESA... A cohort, 6,600 folks. And you're looking for incident cardiovascular events over time. And then you're saying, okay, I'm going to adjust the usual co-variants; age, gender, ethnicity, medication use, do the adjusted analysis. Okay. Now does... As a model of variable univariate association, does LPIR associate significantly with incident cardiovascular disease? Yes.

Dr. Cromwell: Does LDL particle number significantly associate? Yes. Now, they're also related to each other, right? Through insulin resistance. So one way to remove this is

put them both in the same model. And if you put them both in the same model and they're telling the same story, they cancel each other out. One is no longer more significant, or predictive than the other. And when you put them in the same model, LDL particle number remains significantly, independently predictive of events and LPIR does not. What that means is, that a large part of the atherosclerotic risk is being manifested through the lipoprotein axis, in the insulin resistant state.

Dr. Cromwell: So, back to first principles, the more bad things you have going on, the worse you are. If you have high particle number and insulin resistance, and for insulin resistance with its associated inflammation and everything else, yeah, you're in a bad place. I don't have those things. I just have high particle number. Am I still in a bad place? Yes. And how do we know? Look at FH.

Dr. Cromwell: FH, these people only have a problem with a receptor access disorder of some type, which impedes their ability to clear LDL. And in the homozygous state, their numbers are crazy high. And as you know, there are lots of examples of severely diseased... I'll give you, what was it, two weeks? Two weeks ago, I had a lady come to me with a one in a million form of homozygous familial hypercholesterolemia. She has the exact same punitive defect, times two, on her gene sequencing.

Robb: Wow.

Dr. Cromwell: That means that mom and dad both gave her the exact same FH gene. That's a one in a million thing. She has horrible vascular disease. She's gone through a bypass surgery, she's gone through aortic surgery. When she was under the knife for aortic surgery the surgeon said, "I tapped on your aorta with my forcep, and it sounded like a PVC pipe."

Robb: Wow.

Dr. Cromwell: This lady has multiple vascular beds, horrifically involved. And all of this started at a very, very young age, right? So there's the example of somebody who has bad LDL for a long time and blew up. And she's not insulin resistant. She doesn't have co-morbidities, right? You layer those things on top of them, it's even worse. But what I'm saying is that there is not only pathophysiologic data, Mendelian randomization data, all the elements of causality are there. You worry in the context of how bad for how long? If you have a bad number, the first thing you have to tell me is how long has it been there? Next thing you have to tell me is, are vessels showing wear and tear and atherosclerosis already? You tell me those two things, I have context to help you do something with this particle number. And the urgency is really, have I intercepted somebody with disease in progress?

Dr. Cromwell: I'm not worried about preventing something, you have something. Versus somebody who, somehow this is a newer problem. And I don't have to worry about it quite so much. The other extreme... And the guidelines actually give you a get out of jail free card in one respect. And that is, if you're over the age of 75 with a zero coronary calcium, you're given a hall pass for whether you take statins for five years. They de-risk you. It's called de-risking, right?

Dr. Cromwell: I had a lady come to me, early eighties, 81, 82. And she said, "I went to my primary and he tried to put me on a statin, I didn't want one, so now I'm here."

And I said, "Well, what's the rest of the story?" "I have a very high LDL cholesterol." "How high?" "About 200." "That's pretty high. When did it start?" She said, "You're the first person to ask me that question. I get a yearly physical, have for years." She went digging in her bag and she pulled out a binder with lab tests. And she went back, this was something that started five years ago. Prior to that she had LDL cholesterols in the 120, 130 range.

Dr. Cromwell: So, she jacked up very recently. And I said, "Well, let's get a coronary calcium score." It was zero. I said, "Well, guidelines say that a zero coronary calcium at 75 puts you in a less risky bucket. Now, what we need to do is understand why your number's not right in the first place." And you already called it, she was hypothyroid. And she developed hypothyroidism some years before, but it was within about a five, six year period of time. And that was the elephant in the room.

Robb: Fascinating, so interesting. Okay, that helps a lot. Oh man, do you want to talk about the homeoviscous adaptation to dietary lipids paper? Like, that might carry us through for this episode, that's liable to be a goodie.

Dr. Cromwell: Oh yeah, yeah. So, I read that paper with interest. And it basically correctly identifies that a lot of cholesterol is in plasma membranes. That that is a huge repository. And they correctly identified that it is a very volatile pool, in that depending on the chain link of your fatty acids, whether you're polyunsaturated or saturated, you change the fluidity of the membrane. And cholesterol actually serves as a buffer to maintain membrane fluidity.

Dr. Cromwell: So in that respect, we're constructing a very interesting story, where we eat different things, different triacylglycerols are being presented to our tissues. Different types of fatty acids are being incorporated into our plasma membranes. Our plasma membranes need to maintain their normal function, including fluidity. It needs-

Dr. Cromwell: Membranes need to maintain their normal function, including fluidity. It needs to be buffered by cholesterol as we change the composition of fatty acids in our cell membrane. So all of that's true and it's sounding very interesting. So they take the next step and say, "Okay, well, how does that cholesterol modify itself? How does it either increase or decrease in the cell membrane?" And they correctly say that it has to do with the endoplasmic reticulum that organelle in the cell, which is responsible for sensing and responding. And so to maintain fluidity, the cell has sensors and it says, "Oh, I need more cholesterol." The signal goes out and the ER up regulates SREBP, it makes more cholesterol. It also upregulates LDL receptors to pull cholesterol and it's a tandem response. I both make more, and I import more. And I do that so that my plasma membrane has the amount of cholesterol necessary to maintain fluidity and function.

Dr. Cromwell: And once that's done, it turns itself down. Okay, we're good now. Right. We're good. And then senses and responses, and as things need to be adjusted either down regulates or up regulates in real time to maintain function of the plasma membrane, the cholesterol content of the membrane, the fluidity of the membrane, et cetera. So that is a very true and dynamic statement. So then the question is, well, what's the limit of that. And at what point does this get disordered? We're back to the idea of disordered regulation. So this regulatory states are what we are seeking to understand. And is this a way to try to explain a dysregulated state? Well, a couple of interesting factoids, about 40 to 45% of

the cholesterol we have is in our plasma membranes. All right, now is all the cholesterol in our plasma membrane, bioactive and available for this process?

Dr. Cromwell: The answer is no. Well, how much of it is stoichiometry and restricted to complexes, cholesterol rafts, and other things where it's associating itself with things in the plasma membrane. And it's basically stuck there and it's not active and it's not mobile. That's 85% of plasma membrane cholesterol, 85%. 15% of plasma membrane cholesterol is bioactive and available for this sensing and response. So that creates a different story already. Right? So if that's true, then we really don't have the situation where there's a huge bulk flux of cholesterol. Cholesterol is actually a buffer. And if you think about buffers, you don't take a lot of buffer to stabilize the system. It takes very little buffer to stabilize the system and cholesterol is a buffer and it takes very little change in order to remedy a fluidics situation or a functional situation. So the actual amount of cholesterol needing to be increased or decreased is much lower of magnitude than inferred by that paper.

Robb: Gotcha.

Dr. Cromwell: So then the question is, okay, how can you accommodate that amount of adjustment, which is much smaller than at first anticipated? Well, you do it by synthesizing more and increasing your import and doing that is something that is within the normal physiologic range and function of a cell. So if you suddenly have big, big, big poof of saturated fat ratio and you suddenly need much more cholesterol in the membrane, well, the much more is a relative statement because the absolute amount that's even available for movement is 15% and the amount of incorporation to maintain functionality and fluidity is not that much. So now we're able to accommodate that, yes, by increasing our synthesis, yes, by increasing LDL receptors. But it doesn't go off the rails. We don't have to triple, quadruple, really jack up our LDL receptors to some Herculean level.

Dr. Cromwell: So within the context of normal physiology, just from what I've said, it's unlikely that we have this need for LDL particles to be present in large amounts, floating around as a ready response Minuteman force to give cholesterol immediately to cells, or they lose the integrity of their plasma membrane and we're in real trouble. So that's kind of the thought and the paper is that, at the end of the day, LDL particles could serve as a Minuteman ready response, giving cholesterol when necessary. And because cholesterol is so dynamic in the membrane and so critical for membrane function, we absolutely, positively have to preserve that at all costs. So part of that I would agree with, and part of that, I think just from the stoichiometry, doesn't lend itself to a good adaptive mechanistic situation that we're likely to encounter very frequently.

Robb: Okay. Okay. Great. Great. That's a wonderful unpacking of that. Thank you. Let's see here maybe just, and I think that this one really is not germane any longer. "What's the difference between the diabetic risk report and the cardio metabolic risk report," that has basically been nested all together where once the cardiovascular part and the diabetic part were separate, now that is all nested together. Am I correct on that?

Dr. Cromwell: Yeah. Well, how we got there is just kind of an exercise in practicality. So, what we chose to do was to say, we want to take the 40 pieces of jigsaw puzzle and put them together and we want computers to do what they do well. The same thing, high-speed, time after time. So in order to build that from nothing, which

we chose to do, we chose to hire good people at programming and to develop a HIPAA compliant, highly secure self-contained entity, if you will call it that, that is capable of taking all the right information, all the combinations and permutations and giving us the right answer one patient at time very quickly. So to get there, you have to kind of take bite sized pieces. You can't eat the pie in one sitting. So the way that we chose to do that was to make the diabetic report, the first proof of concept that we could do this because all of that information would then be necessary with additional information to come up with the cardio-metabolic risk report.

Dr. Cromwell: So as our first effort, we had to build the domain, build the environment, have the right specs and functionality, security, et cetera. We then had to have a more defined set of data that had to be identified, brought in, handled, and a report generated. And that's how the diabetic report came to be. At the end of the day, as you said, the diabetic component of the cardio-metabolic report is still there, but it has the rest of the story wrapped around it, as Paul Harvey would say. Now, the complexity of this is really beyond me because I'm not an IT guy, but I can tell you a hundred pages of code and algorithm later is what we got with cardio-metabolic risk report.

Robb: Wow. Wow.

Dr. Cromwell: It is a daunting undertaking. And my partner, Matt Martin gets all the credit for working with the programmers to make that task, something that has come to pass.

Dr. Cromwell: And, and our goal was scalability. Build it at the beginning to scale so that you can do thousands of reports a day, thousands. How many thousand? I don't know, you find one with 10,000 a day and some huge number where it's highly automated and it just clicks out the right answer every time, because all the inputs have been stress tested, all the logic has been stress tested. And when you do this, you find things, got to go back and fix this up. You've got to fix that. It's also dynamic enough to respond to new data as time goes on, and we will find new risk enhancing factors, we will find different ways data have to be integrated to be compliant with outcomes and guidelines. And that's what we've chosen to do. And the other thing that we imposed on ourselves was some discipline of, get there with the best outcome proven biomarkers and the fewest number of outcome proven biomarkers.

Dr. Cromwell: And to me, that's very important. I think that the challenge in clinical medicine is that there is an unbelievable amount of information out there and a tremendous amount of laboratory data, for example, that doctors get. So is more better, just because you can get more? Not necessarily. I've seen big, bulky lab reports that have lots and lots of data. Let, say five or seven different inflammatory biomarkers, for example. Well, are they all necessary? And if so, why? And you're saying, "Well, some say this and some say that, and this informs this, and that informs that." Well, what happens when they disagree with each other? Or what happens when you have three of your markers saying one thing and the other marker saying something else? Now you're confused.

Robb: Right.

Dr. Cromwell: And why did you have to go there in the first place? Just because it was available, because every one of them had strong outcome proven value? Or

because there are limits in our understanding, and we're hoping that emerging factors would fill in the gap with data yet to come.

Dr. Cromwell: And I think there's a lot of the latter, right? And so we chose Glyc A for that reason that it has exquisite biologic state stability. It is coming from a family of inflammatory proteins, not just one. Its biologic variability is less than 10%. Actually less than 5%. Hs-CRP has a biologic variability of 30 to 50%. Hs-CRP has a high gender bias, 40% higher in females. Glyc A less than 10% gender bias. You look at outcome associations, Glyc A much more significantly associated with mortality, with diabetes, with heart attacks. So these are the reasons why we get a lot of value out of one biomarker and it overcomes limitations of many individual inflammatory biomarkers without the need to get five different tests, which may or may not be concurrent with each other.

Robb: Love it. Love it. Let me see here. I think that we ended up... If one is stuck with just conventional testing, which I push back on that I'm like, you're not stuck with it anymore. You've you've got precision health reports, but if somebody has that as their main go-to... We do have a lot of folks that are international. People are in Canada, Europe. They don't really have access to even the NMR as just a beginning place. What are some, if you had to work within those constraints, triglyceride to HDL ratio, what would you look at as kind of a short list again, to your last question, there's a million different things we could look at. If you had kind of a short list of things, somebody doesn't have access to the NMR. What are some things that you would have folks look at?

Dr. Cromwell: All right. So let's build out from the center of the bullseye. Let's start with the lipid panel. Everybody's got a lipid panel. So, that's going to be easy. What I would tell you is the two things on a lipid panel that could be helpful would be triglyceride HDL ratio, and non-HDL cholesterol. Those two things carry a lot of weight. Now why? Triglyceride HDL ratio, as you know, has an association with insulin resistance. So higher ratios infer more insulin resistance, three and a half or more is kind of that number that people look at as being indicative of a potentially insulin resistant state. So if you're looking for just a marker and say, "I wonder if that could be the case." Now it is not as sensitive as LPIR score is. Now just to put some brackets around that, one of the things we did with the LPIR score was to kind of stress test it and its ability to predict incidence diabetes.

Dr. Cromwell: So if you look at MESA, PREVENT, CARDIA, Women's Health, large population studies. Okay. Does LPIR predict incidence diabetes? Yes. What else does? And there's a laundry list. There's a whole laundry list of things, right? And many of them overlap with the triglyceride HDL ratio. Insulin, glucose, HOMA-IR score, all sorts of things. Well, let's do it this way. I have NMR LPIR score. If I adjust that for glucose, does it by itself continue to predict? Yes. I adjust for waist circumference. Yes. Adjust for body mass index. Yes. Adjust for triglyceride. Yes. Adjust for HDL cholesterol. Yes. Adjust for triglyceride HDL ratio. Yes. Adjust for insulin. Yes. Adjust for HOMA-IR. Yes. It's amazingly robust because it is the best proximal early indicator, physiologically of insulin resistance. Even before insulin goes up, even before glucose goes up. But if I didn't have it, if you're taking it away from me, triglyceride HDL ratio is one of those things I could use. Particle number, we've talked about on previous podcasts, but LDL is a particle.

Dr. Cromwell: LDL is not cholesterol, LDL particles carry cholesterol, but the cholesterol in LDL can be a lot or a little. Therefore, how many particles you have may or may not

be well reflected by your LDL cholesterol level. Well, if the cholesterol is not in LDL, where is it? It has been redistributed through the cholesterol, ester transfer protein, to other APO B containing lipoproteins and HDL, so it's been redistributed. The APO B pool is what non HDL cholesterol gives indirect visibility to. So total cholesterol minus HDL cholesterol is the cholesterol in all APO B containing lipoproteins. 90%+ percent of which, are LDL. So what you find is that there can be people with an LDL cholesterol, which is at one level and a tandem non HDL cholesterol, which is much higher. That is an inference that you have high particle number. Now what's the limit of that. If you look at particle number, either by APO B or LDL particle number, and you compare that to non HDL cholesterol, how frequently are those two values, particle number and non HDL cholesterol discourt? 40% of the time.

Dr. Cromwell: So it's not bulletproof, it's better, but it's not bulletproof. Right? So for our lipid panel to give something better than just total cholesterol, triglyceride, HDL cholesterol, LDL cholesterol, the two things that you could do better with your lipid panel, in my opinion, triglyceride HDL ratio, non-HDL cholesterol, but they both have limits, as discussed.

Dr. Cromwell: Now, if you wanted to take a step further. Particle number, there are two ways to do particle number. APO B, that is a commodity test in many laboratories, or you could get a LDL particle number by Innomar. Innomar, like the profile report, depending on where you get, it can be different prices. The price that we get it for is probably different in price other people get it for, so that's an issue for some place. But I will also tell you that as of today, as we are recording, we have an APO B version of the Precision Health reports cardio metabolic risk assessment. So there are people out there who say, "I like APO B more than LDL particle number." That's fine. I'll give you an APO B version. And it still has baked within it, LPIR score, LPa, Glyc A, all that's still in there. But if there are people who have a preference for one type of particle number measure APO B versus another LDL particle number we can accommodate that.

Robb: Do you think we'll ever see an APO B IR score analogous to the LPIR score?

Dr. Cromwell: No.

Robb: Okay.

Dr. Cromwell: And the reason is because the LPIR score is informed by absolute numbers of large VLDL particles, small LDL particles, large HDL particles, as well as VLDL size, LDL size and HDL size. So those constituents are what make up the LPIR score.

Robb: Gotcha.

Dr. Cromwell: And as a result, it's its own thing. But what I do want to help people with is the idea that getting these tests doesn't have to be uber expensive. It can be done simply, and you don't have to sacrifice the added value and information just because A) you're looking for something that's not real expensive or B) you have a lipid panel, and you're trying to make the most you can with it. There are limits with what you can do with lipid information because lipoproteins are their own thing. Lipids are things carried in lipoproteins. And as you remember, back in the sixties, Don Fredrickson actually opined that unfortunately lipoprotein problems are being given visibility as a lipid phenotype, and we would do much better if we would just look at the lipoproteins directly to understand what's

wrong and how we can fix it. That was true in 1967. It's true now. And almost 2022, we don't have to accept "maybe," when the answer can be done very simple.

Robb: Great. Bill, maybe as kind of a wrap-up question or close to it... Are you folks looking down the road? We do have a lot of listeners from Canada, Europe, outside the United States, will there ever be a portal where folks can upload their data and then have it run through a similar, the APO B version of this. Will there be an opportunity for folks to upload data and then get a similar report generated versus going through specifically the precision health reports where the blood draw is ordered and that whole process.

Dr. Cromwell: So things that we can do, we can accept laboratory data from individuals, if they have labs in their chart, for example. We can do that. It is more direct and more reflective to have a contemporary blood draw, where we have the analytes necessary to give a fully informed report, that's our preference. If you don't have an LPIR score, there's no way for me to handle certain parts of the report without an LPIR score. I can't give you your diabetic risk, I can't inform you of what your magnitude of insulin resistance is. I can use other elements of the report. So I would seek... My solution would be, how can we get a lab sample drawn so that we're getting the information needed for the full multi cardio metabolic report. And there are ways to do that in Canada. There are ways to do that throughout the United States, Alaska and Hawaii.

Dr. Cromwell: There may be ways in the future to do that in Europe. I don't have a way right now, but there are ways that we could consider trying to block and tackle our way into that. As you know, Liposcience was able to accept samples that were archived and hard frozen, minus 80 samples, for reference studies. So we know that samples can, under unusual situations, be archived and thawed and used. We're not in the process of doing that, but, just saying that can be done. Really the limitation currently is there's a six day window of time from blood draw to being analyzed in order for lipoproteins to be considered within window, within range and not rejected. Beyond six days, the sample is deemed to have aged too much and will be rejected. So you've got a window of time to get the blood drawn and analyzed, and that can be accommodated in North America, that can be accommodated in Alaska and Hawaii, but it would be a challenge unless somebody were to hop on a fast jet, go across the pond and get it to us.

Robb: Right. Okay. Okay. I did see some noise about the UK potentially having the LPIR score available soon. So we'll see if something comes about for that. Awesome.

Dr. Cromwell: Well, this would be something that, if we had that, so to your point, if you've got LPIR score, if you've got the NMR lipoprofile report, either it's APO B flavor or it's LDL particle number flavor, it could be LPa, Glyc A, glucose, we can make much of this, right. But at the end of the day, our motivation's much like yours. And that is, everybody's on a journey, everybody's journey is different, and we intercept people at different parts of the journey. What I really, really want to do is make it easy for people to know where they are, identify as early as possible dysregulated metabolism, so that we don't have to wait for an event to get somebody noticed and then make the type of lifestyle interventions that can have huge success.

Dr. Cromwell: Reserve medications for where they're needed. They will be needed in many people somewhere along the way. We don't start there, we stop there. I tell my

patients, "Medicines are mops and brooms. They clean up your mess." But the less mess you have, the fewer mops and brooms I need. I've got five kids they're older now, but I remember the days of little hands, little feet and big messes. I can either be my kid's janitor, or I could help them learn how to not make a mess. And that's the same sort of thing. If we can help our patients learn how to not to make a mess, then they'll do a lot better with less medicine. And what medicine they take will have a greater likelihood of success.

Robb: Love it, love it. Bill. This was phenomenal. And we did it in an hour and 43 minutes. So not too, too long there. Nikki and I are going to do an intro outro on this, but is there anything else... That was a beautiful closing, we might just wrap up there, but anything, any final thoughts there? That might actually be the cherry on the sundae. Just that closing right there.

Dr. Cromwell: Maybe it is. I think there should be a lot more people like you and folks in Healthy Rebellion to kind of stir the pot, so to speak. We got to get out of a sick care system into a well care system. It takes a lot of momentum to get through that. I mean, the inertia is huge, right? But congratulations for all the work you've done, appreciate the work you do, and everybody in The Healthy Rebellion, I think those folks are highly engaged, highly motivated, wonderful folks, have great questions. Unfortunately, we don't always have data to answer the questions directly. We do our best, but you know, thoughtful people will ask leading questions and sometimes we run out of data road and when that happens, we just say it, the road ran out, but we deal with what we do know and we move forward from there.

Robb: Love it. Love it. Awesome Bill. Well, I'm sure we will get more questions and we'll probably come back and do this again at some point.

Dr. Cromwell: Well, we should make it something of a more regular thing.

Robb: Let's do it. Let's do it. Awesome Bill. Thank you so much. Take care.

Dr. Cromwell: Sure, thanks.

Robb: So are we good?

Nicki: I think we're good. That's a meaty one.

Robb: It's a spicy meatball, lots of material. And the funny thing is as thorough as we tried to be, we were still an hour and a half on this. I think when you have a podcast, this information dense, like doing a Joe Rogan three hour deal just doesn't make sense. I am burned out by then. I think Bill could go for eight hours talking about this shit and not even blink during the thing, but we will do more, as more questions emerge like Bill and I realized that there was a question around, well, where does HDL plug into this thing? And, oh man, we should've grabbed that. So we already have a list brewing for another installation of yet another follow-up with Bill. This topic is huge, but this cardio-metabolic screening and the diabetes risk assessment that the Precision Health reports folks have put together is phenomenal.

Robb: And it really provides an insight into your disease risk profile that is nigh impossible to get. At the beginning of the interview, Bill made the point that you could end up in these really funny scenarios where say, if you have eight

different categories and it's low, medium or high risk, and you could be on the cusp for three of these things, an untrained individual could look at that and be like, "Oh, you're fine." Or conversely, you could end up with three of these variables kind of in the medium risk category. And an untrained individual would look at it and be like, "Oh, you're screwed." And in both situations, they're wrong because there's context to, well... If one is way over and the other isn't, and this is part of what Bill and his partner, Precision Health, Matt, have been working on is getting some algorithms to really sort this stuff.

Robb: But then there is a meat bot, Bill and other folks, that look at this and give you a really good sense of where you are, provide a roadmap for what to do next. And then we can get in and tinker with diet and lifestyle and really milk that for as much as we possibly can to modify this disease risk potential. And then if there is a need for a pharmaceutical, somewhere in that line, then you also are operating from a spot where you've done all the stuff that you need to do anyway... Improving metabolic health, improving inflammatory markers, blood glucose levels, all that stuff. And then you can also really have a sense of what your risk appetite is for doing something like a statin or a PCSK9 inhibitor, even some of the other things like Zetia, which can cause you to absorb less of the dietary cholesterol and stuff like that. So anyway, really good show, super-stoked for Matt and Bill to do the things that they're doing and we will have him on again.

Nicki: Yes we will. And again, that link, if you are interested in that in doing the cardio metabolic panel is precisionhealthreports.com and the code Rob Wolf, R-O-B-B-W-O-L-F. We'll give you 10% off of those risk assessments. Remember if you're a member of The Healthy Rebellion, don't use that you've got special pricing inside the community, and just a final shout out for our sponsor of today's episode, LMNT. You can get all of that salty goodness, stay hydrated this summer. It's going to be very, very hot here in Montana anyway, so I'm sure it's going to be even hotter elsewhere. So you can grab that at drinkLMNT.com/robb that's drink L-M-N-T.com/R-O-B-B. Everyone, have a fabulous weekend, a fabulous and safe 4th of July, and we will see you next week.

Robb: `Bye everybody.