KRESSER INSTITUTE
FOR FUNCTIONAL AND EVOLUTIONARY MEDICINE

ADAPT Bonus Interview with Mark Newman

Chris Kresser: Hey, everybody. I'm really excited to be bringing you this interview with Mark Newman.

Mark is one of the foremost experts in the area of hormone testing, especially regarding monitoring HRT, reproductive and adrenal hormones. He has designed several hundred novel tests at multiple labs before starting his own lab, Precision Analytical, which produces the DUTCH hormone test that I'm teaching you in this course. Mark has educated thousands of physicians on hormone testing best practices, and he's one of the smartest people I know when it comes to hormones and hormone testing. As you know from the course, I think the DUTCH test is the best available hormone test right now for us clinicians. It offers a lot of information. All of the hormone testing methods have their pros and cons, but I think DUTCH offers the best compromise among all of them, and so I'm looking forward to chatting with Mark about some of the topics we're covering in the course, and I hope you enjoy the interview.

Mark, it's a pleasure to finally get a chance to do this. Thanks so much for taking the time.

Mark Newman: Yeah, I'm thrilled to be here.

Chris Kresser: Before we dive into the meat of this, maybe we can talk a little bit about your background experience, why you ended up starting Precision Analytical, what need it solved that you were seeing wasn't being met with your years of experience in the hormone world.

Mark Newman: Sure. My angle on this whole world of hormones is from the analytical side. I spent some time directing the testing via 24-hour urine, kind of looking at the pros and cons of that, and then moving over to saliva lab and managed probably about a million saliva results and saw the pros and cons of that. To be honest, I just got a little bit frustrated with the limitations of seeing pieces to the puzzle but then always wondering about these other things that we can't see with this particular test. In particular, the cortisol piece is what really drove this. Even though the urine testing opens up the door pretty wide for reproductive hormones to look at metabolites, and those are advantageous, the main thing that drove it for me was the cortisol, looking at the free cortisol picture in saliva and saying that's a really important piece of HPA axis function, adrenal, whatever you want to call it. That's important. Then when I look at urine testing, I have this really improved measurement for cortisol production in the metabolites, and so looking at the advantages of urine and saliva, it took about 10 years to kind of piece this thing together, but we came up with a model where we could look at all that information in one test. It's just made me a lot more confident in feeling like I'm characterizing a patient well, as it relates to cortisol or the estrogens or the androgens, because it's just so much more information on all of those fronts relative to what you typically get. That was kind of the inspiration behind this and getting us started with the lab and this particular type of test.

Chris Kresser: Let's dive into that a little more deeply. We have these different methods of measuring cortisol. We have urine and saliva. Hair is even used, although not very often and not at all, at the moment, outside a research setting, as far as I know, and then we have serum. Let's go into the pros and cons of each of these methods, especially from a clinical perspective, starting with serum.

Mark Newman: Sure. With serum testing, the alternative crowd, at least certain sections of it, I think, are a little hard on serum testing. I think serum testing works great for most things. We're never going to live without blood testing because I'm not doing CBCs and blood chems and a stool sample anytime soon, or saliva or whatever other body fluid. There has to be a need for blood. When I want a thyroid panel and I want to look at T3, T4, and all these sorts of things, I think that's the best place to go. And with the reproductive hormones, you're still on pretty solid ground. With testosterone, you can look at total and free. Estradiol and progesterone. They're well measured in serum, I think. If I want the metabolites for the reproductive hormones, it gives me a little added value, looking at the urine, but it's the adrenals where serum testing really falls short, in that I look at a total cortisol at one point in time. If I move from total to free, the literature would tell me I've done a good thing. That's a better marker for your status as it relates to cortisol. If I look at free cortisol over time, now I've improved even more, and that's where there's been this migration with adrenal hormones to saliva testing, and then there's this third dimension that we're bringing to the table, which is a better marker for the overall production via the cortisol metabolites. So you're really three steps removed from a more comprehensive picture of cortisol with serum. For everything else, I think you can get a pretty good handle on a lot of things in most situations, but it's really the adrenals where serum just doesn't have enough information in most cases to help us.

Chris Kresser: Right, not to mention the fact that you're going to have a really hard time getting a patient to go to the lab four times in a single day in order to get the diurnal rhythm of cortisol production, which turns out to be pretty important, as we cover in the training program.

Mark Newman: Right.

Chris Kresser: You can have normal overall cortisol secretion over a 24-hour period, but if you have really high cortisol at night and a blunted cortisol awakening response, that's problematic, right? And you're not going to get that with serum testing.

Mark Newman: Right, and it goes, of course, further than that because the blood draw itself is a stressful situation, you're measuring a stress hormone, and then you might have a bedtime cortisol, but it's a total cortisol. Again, with most of those hormones, it does well, but you're kind of several steps removed from an ideal or at least an improved situation that we have available to us via other tests. That's really where serum is just limited.

Chris Kresser: All right. Now saliva. Let's talk about saliva. This has been, really, the default method for assessing so-called adrenal fatigue. Those who are listening to this interview know that that's a

problematic term, but mostly via adrenal stress indexes, these four-point saliva cortisol tests, which have really been in use for what? Three decades now?

Mark Newman: Yeah, I think the first cortisol test was in '81 in saliva, and it picked up steam in the '90s for research, and rightfully so. It's a better marker of that cortisol pattern throughout the day, and we can look at PTSD, chronic fatigue, and all these different situations where either the pattern itself is messed up or the absolute level is problematic, and I'm sure at some point in this we'll get into the whole CAR, the cortisol awakening response. If you set that conversation aside for a second, the saliva has something there to offer and that's good. The argument that I would make is that if you can preserve that information, provide an alternate that's acceptable, which is what we're trying to do with our model, and then add to it the total of the metabolites, there are a lot of situations where you can really get fooled by just the free cortisol picture if you're not looking at the rest of it.

The other area where, for me personally having wrestled with trying to develop saliva assays over the years, it falls short is there's this sort of unintentional bait and switch, where you say, look, I can look in the literature and I can show you that salivary testing of free cortisol is an improvement because it's free cortisol. Then you move to the estrogens and people intuitively say, well, OK, is the estradiol free as well? Yes. OK, well, then that must be improved as well, but there's 10,000 times less estradiol than cortisol, and the methods themselves just struggle to get a good accurate number, so I think the reproductive hormones, the analytical work is just not good enough. I would much rather do a serum test.

With the urine I really like it because you get a better marker of that hormone, and then you get also the metabolites, but for me, I think there are just too many pitfalls for reproductive hormones, so to me, saliva, the best use of it is for the free cortisol, but as I began to dig into that, to me, it's better than a serum test, I think, for cortisol, but if you can add in the total of those metabolites, you can just point to so many cases where it reshapes your characterization or your thinking of who this person is with respect to cortisol, and I think it's a pretty significant difference. So saliva is good for cortisol, but I think you can improve on that model, too.

Chris Kresser: Yeah, I'll be going into a lot of detail about this in various parts of the HPA axis unit for those listening, so we're not going to belabor it here, but of course, one of the major issues with saliva cortisol testing is it measures only free cortisol, cortisol that's unbound to a protein carrier, and while that is the only form of cortisol that's available that actually has cell-signaling effects and activates the cellular transcription response, it's not the best marker of overall production, and we're going to be talking about situations where there's discordance between free and total cortisol, either low free cortisol and high metabolites, as we would see in obesity or insulin resistance, or the opposite situation where we see high free cortisol and low metabolites in something like hypothyroidism or impaired liver function.

But there are a couple of other problems with saliva testing, too, which are the lack of standardization out there with all the different labs. We have different labs using different units,

and then we have different labs giving different instructions for how to do the test, which can have a major impact on the results.

Maybe one of the best ways to talk about this is the split sample that we did. You remember this, Mark. We had a patient, and we decided to do three different tests on the same day. We did a DUTCH urine test, we did a BioHealth saliva test, and we did a LabCorp saliva test, and we were interested in seeing how close they all were—or not close, in this case! First of all, we had to convert the units for BioHealth and LabCorp because they don't use the same units.

Mark Newman: Right.

Chris Kresser: So that was one thing that was difficult about it.

Then second of all, we saw that the lab range for LabCorp, the difference in the low end of the lab range for the morning and noon samples was twenty-fold. Participants who are listening to this know that functional ranges are usually tighter than conventional ranges, but I've never seen a functional range that's twenty-fold tighter than a conventional range.

And then we have the issue of cortisol awakening response, and like you said, we're going to come back to that, but more than 50 percent of the total day's cortisol is produced in that first 30 or 45 minutes, so what happens when the lab just says, "Yeah, take the morning sample within the first two hours," and the patient wakes up at 6:00 and they take their first sample at 8:00? What's going to happen there?

Mark Newman: Yeah, it gets tricky because even when the labs do a good job, whether it's a urine lab or a saliva lab, explaining things, we see all kinds of things. We even have a dried urine sample, and we have people send in their samples wet. I'm like, it's right in the name "Dried Urine Test."

Chris Kresser: Yeah.

Mark Newman: People will make all kinds of mistakes, and that's a part of any lab test. But I think with the cortisol you have some particularly troubling situations. I'll give you an example. A doctor calls me and says, "Look. I have a patient who tested low for salivary cortisol," but when you looked at the results, really it was just that morning result that was low. They put him on hydrocortisone and then got a call from an endocrinologist who said, "You know, this patient is in this Cushing-like situation because you put him on this hydrocortisone," and as I got to looking at it, the collection time was 9:30. And I said, "Was that, by chance, a Saturday?" They said, "Yeah, it was a Saturday. Why do you ask?" I was like, "Well, we see this type of lab testing frequently. You go to your doctor on Wednesday and get your test kit, but you have to go to work on Thursday, you have to go to work on Friday, and you get up every day at 6:00, 6:00, and then you hit the weekend and you wake up at 6:00 and your body is trained. There goes that cortisol awakening response oftentimes—not always, but oftentimes—and then you go back to sleep, and then you get up and go, "Oh, yeah. I have to do that lab test." So you even followed the instructions. "I literally

just woke up and got up at 8:30 or 9:00 or whatever, and I followed the instructions. I tested half an hour later." Well, that awakening response is big up and it's big back down, and then you start this gradual decline the rest of the day. So if you test two hours after what's typically where your awakening response is and you just miss it, you can get misdiagnosed. Yeah, those types of things become problematic, and then the references ranges, you really have to kind of dig through the situation. If I'm using LabCorp, it's going to be pretty different than if I'm using this "functional" test, and I've seen a number of cases where labs have cut their ranges to where otherwise healthy people, like 30, 40, 50 percent are being diagnosed as being low because the ranges are so tight. Or maybe, I've seen this situation where someone switches from one method to another method, and those numbers dip and the ranges stay the same, and then you can go sometimes months and years and not realizing you're over-reporting this "You don't have enough cortisol" message. And that's not a saliva thing, per se. That's really anything outside of blood when you're talking about hormones because you're really dependent on the competence of the lab way more so with urine and saliva testing than with blood because it's really standardized and it's easy to do. It has some limitations, but that is an advantage of blood testing. I tell people if it can be done well in blood, there's no reason not to use that because it's standardized so much better, but there are tests like this where you have to get into that esoteric world, but when you do so, again, you're putting your hand, so to speak, into the hands of someone else, and their competence really affects how useful it's going to be in terms of just where you end up.

Chris Kresser: Right, and just as a follow-on, the numbers that we compared from that split sample with BioHealth and LabCorp were actually pretty close. Particularly the waking and the morning samples were right on the line, and then the afternoon and evening samples were a little bit off, but they were still in a relatively comfortably close range, but it was the reference range that was so dramatically different. The patient was extremely low on BioHealth and was completely normal on the LabCorp reference range. That's just an illustration of how much these ranges can have an impact on both the clinician and the patient's perception of what's going on.

Mark Newman: Right, and I think it's important to mention that that can be because—solely because—a conventional lab has too-wide ranges, or it can be because this functional test that you have is not set up or standardized properly, so the error in the fact that you're getting the same number, but a different message can be in either or both camps. I don't want to paint this picture like, "Yeah, if the saliva labs would get their act together!" It's a tricky kind of thing.

Chris Kresser: Yeah, I'm not assigning any fault here. I don't even know where everyone's getting their ranges from.

Mark Newman: Right.

Chris Kresser: And it's possible that, in the case of the functional saliva labs, that the ranges have been influenced by the concept of adrenal fatigue and the idea that if we narrow this range, we'll catch more people with low cortisol, operating from the assumption that low cortisol is the fundamental pathology, which as all the people listening here know, I'm going to argue is not really

the primary pathology in terms of HPA axis dysfunction. High cortisol is probably more likely, and then things like disrupted cortisol rhythm or impaired cortisol signaling or elevations in binding proteins or these other brain and central nervous system and tissue-specific regulatory mechanisms, downregulation of corticotropin-releasing hormone receptor sensitivity and the things that we observe in PTSD that even when cortisol is low or someone is experiencing the physiological effects of low cortisol, it's very likely not because the adrenals are fatigued and unable to produce it.

Mark Newman: Right.

Chris Kresser: So just as a placeholder, saliva is murky. It's certainly a valid test method, but there are a lot of challenges and issues with it, which we've covered. Before we move on to urine, let's just quickly talk about hair. It's not a major player at this point, but what's some of the potential that hair has for cortisol?

Mark Newman: Well, I think the appeal is just the index over time, right? In a lot of cases, it's better to know your A1C than your blood sugar right now because it's an index over time, and hair has that potential, but it's a tricky sort of thing because the cortisol is made in the local environment before it's put into the hair, so they're going to have to really research it well to figure out what it means. But it's interesting because we say obesity is this interesting situation where the saliva tends to be low and our free cortisol tends to also be low, but the metabolites are so super high. The blood goes down, too, in obesity a little bit. It definitely doesn't go up, generally speaking. Hair is that other location where you see gobs more cortisol being produced and in the hair, so it has potential, but I think especially because the cortisol is made locally, I think there's going to have to be substantial research before we know exactly how to interpret that, because if you're used to testing heavy metals in hair, which I'm not, I just know some people who are, and boy, there are some real complexities of what causes spillage into the hair and what doesn't, and there are some counterintuitive conclusions sometimes, and so I think it has a lot of promise as a long-term indicator. It's probably not ready for primetime yet, but it's really interesting.

Chris Kresser: Yeah, as a sort of A1C for cortisol, it is interesting and could clinically give us a way of tracking changes that we're making over time, but I agree with you particularly because we know that there are not only CRH receptors in the skin, which would include the scalp, but there's some research suggesting CRH is produced in the skin as well as in the gut and there's like a mini-HPA axis in the skin. There's a possibility in my mind then with that that there could be local differences. There could be cortisol that's being produced locally in the scalp that's not necessarily matching what the systemic production is, so, yeah, we definitely need some more research on that.

Mark Newman: Yeah, and I think that just highlights the fact that we are midstream on this concept. I think that's a really important thing for people to realize. They go into educational situations and you might get educated on adrenal fatigue and it's, "If this, then that, and here's why," and people move along as if these are settled, the-book-is-written sort of topics, and boy, it's a complex thing, and

there's some really fascinating research that is still increasing our understanding to a pretty significant degree and pointing out the fact that there's a lot more to learn.

Chris Kresser: Yeah, OK, so here we are. We've talked about serum, saliva, and hair. Now let's move on to the pros and cons of urine, and let's first talk about 24-hour urine because that was typically the way that cortisol was measured with some of the earlier hormone urine testing.

Mark Newman: Right.

Chris Kresser: And then let's talk about the downsides of 24-hour urine that dried urine addresses.

Mark Newman: Yeah, 24-hour urine is a nice test, in that it captures the entire day, so if you have an ebb and a flow of hormones, you're going to average that out, which, for something like a reproductive hormone, is a nice thing. When you come to cortisol, obviously the ebb and flow of cortisol is in and of itself a significant measurement of how that cortisol is changing. The diurnal pattern, that up-and-down pattern, is the same in urine. You just have to go get it. You have to time your samples and your individual measurements in order to get it. The other thing that people don't usually realize about cortisol in a 24-hour urine is a lot of the labs in the functional space don't actually test free cortisol; they test total. Cortisol is unique, in that when I look at estrogen, it is only in urine as a conjugate, as a water-soluble conjugate. When I look at cortisol, it's both. It's free and it's conjugated. So the easiest thing for the lab to do is to measure the total for everything because that's what we want for the reproductive hormones, but when you go look in the literature, you will not find a paper. You'll have to dig really hard to find a paper that talks about the measurement of the total, free plus conjugated cortisol in urine, yet that's what most of the labs do. Genova—I'll tip my hat to them—if you want cortisol in a 24-hour urine, you have to pay for an extra test from them because it's a separate measurement because they—and again, credit to them—are measuring free cortisol, whereas other labs … and I'm not talking about Quest. That's where 24-hour urine free cortisols come from, right? Conventional medicine. But when you get into functional medicine, a lot of those labs are measuring total cortisol. Well, most of it's not free. It's a different test. You have to work harder, it costs more money, and all that. So what we're doing is adding four of those measurements of free cortisol, which I like a lot better, but that's something lost in most 24-hour urines. Not only do you lose the pattern, but to be honest, it's not the right measurement, and the two don't correlate to each other from the work I've done. I think that's a big misunderstanding that people have with a lot of the urine testing, but the other downside is, of course, just getting people to do it. You have to collect on day 20 of your cycle, and you work at Macy's, and here's your urine jug to carry around all day. It's tough! That's problematic a little bit. And you know, your cortisol response is different on a weekend. That's why we build our test really with that intention of saying that, if you can, it's built so that you can do it on a weekday because that's what we were after with people for the most part. How do you look on a normal day when you're stressed? How is that response? It's not the same on the weekend, so we want to build the test so that it's flexible for that, and with 24-hour urine, it's just a little bit tougher to do that.

Chris Kresser: Yeah, I've seen several studies, actually, specifically looking at the difference between cortisol production during the week and on the weekend as a measure of work-related stress. It's pretty clear that you cannot just do this on the weekend and expect it to be reflective of what your typical weekly stress load is, presuming you work during the week.

Mark Newman: Right. The response in the morning has a lot to do with your perceived stress.

Chris Kresser: Yeah.

Mark Newman: And I'll tell you, you healthcare providers have this classic pattern that I always see. Your early morning surge of cortisol is really big because they have a lot going on, and there are usually stressful practices and this and that, and that perceived stress drives what happens right before you wake up and right after you wake up, and, yeah, it is different on a weekend, so I think that's an important thing to think about.

Chris Kresser: Mm-hmm. So we talked a little about the CAR a couple of times now, which stands for cortisol awakening response, and just to provide a little more detail here, I am covering this, so most folks are going to be aware of it, but before we even wake up, the normal HPA axis activity starts to increase cortisol levels, but when we open our eyes in the morning and light hits our retina and activates the suprachiasmatic nucleus, that creates an even more dramatic increase in cortisol within the first 30 to 45 minutes after we wake up that, as I said, accounts for over 50 percent of the cortisol that we produce in the entire day. When you look at the research on cortisol and its relationship with health and disease, a substantial number of the studies are actually looking at the CAR. They're not looking at four-point diurnal cortisol results. They're not looking at total cortisol levels. They're specifically looking at the CAR, and they're saying, in this disease condition, the CAR is blunted or downregulated. In this condition, it's upregulated or increased. The DUTCH test doesn't get us a true CAR, but speak to that a little bit. What can we do as clinicians to get a sense or even a rough kind of idea of what the awakening response is, using the DUTCH test?

Mark Newman: Well, the irony is that you can't typically get a CAR test from a saliva test either.

Chris Kresser: Right.

Mark Newman: It's kind of funny because it's set up well for it. It's kind of challenging for patients to do. You get a lab person, and they want to do a CAR, no problem, but to get someone to execute it correctly is challenging, but the lab testing is just not set up that way. I think some labs are starting to come around to this in the saliva front, but most people, the instructions say what? Get up, let your cortisol rise, and test at 30 minutes. I've tested myself every five minutes for an entire day.

Chris Kresser: Yeah, I remember you showed me those results. I was like, wow, you were busy that morning!

Mark Newman: Yeah! So for me, it's about five to 10 minutes, and I'm done. It's up there for me. So you test at 30 minutes, and, yes, they're looking at that delta, the change between that first five minutes and that second point, and we're actually in the middle of, right now, a study where we have people doing CARs in saliva and collecting a urine sample right when they wake up and then two hours later, and then the salivas we're measuring at baseline, 30, 60, 90, and 120. So we have five saliva measurements over the same period, and we're looking at the integration of that peak relative to that one urine sample. From the data we have so far, the integration of the peak terrifically well correlates with the urine value, but that still isn't the delta, so I think there is an extra bit of information, not how much cortisol, but what is that relative change? We'll see. When we get it done, we'll correlate the actual CAR to that two-hour urine sample and see how well they correlate. In a lot of cases, if you look at the literature … What was that paper I was just looking at? I forget what they were studying, but they had basically fixed people's flat patterns, and then you could see this big rise of what the CAR had become. And if you look at the people who don't have it and the people who do, capturing the whole period in one sample would actually be a pretty good way to do the same level of differentiation between the haves and the have nots, but it would probably never be a true replacement for a CAR, so there may be a place for that, and that's, I think, an area for the saliva labs to grow in. Again, it's challenging because you only get five minutes to collect that sample.

Chris Kresser: Right.

Mark Newman: But that's also the sample that usually the saliva labs want to use for testosterone and estrogen and progesterone, so it's this kind of logistical limbo of trying to figure out how to do it. I think it's a good thing if it is done, and we are doing some research on that ourselves, as well, to see if it's necessary to do the DUTCH and a CAR or if that morning two-hour sample gives you a pretty good handle on it, to whether it's worth it or not. But, yeah, the true CAR has to be saliva with multiple measurements, and you're looking at the change.

Chris Kresser: Right. You and I have talked about this, Mark, and I will keep everyone posted on these developments. I mentioned in the training a way of using currently available saliva testing kits to do a kind of hacked CAR. The report isn't going to make any sense, obviously, and you'll have to give your patients separate instructions because the instructions that come with the kit aren't going to be correct for doing that, but where there's a will, there's a way. It can be done. The question still is, what additional information is that going to add, and does it add anything above and beyond what we're already getting with the DUTCH test? That'll be interesting to track.

Mark Newman: Yeah.

Chris Kresser: And as we've said, one of the issues, too, is it's hard enough to get people to do the normal four-point saliva test, or even the DUTCH test, right, for that matter, although we've seen really good compliance with DUTCH. You've mentioned some issues where people think they're complying, they think they're doing it right, but they're not. Part of what we're offering in this

training is these FAQs that we've developed for patients that you can give to your patients that explain in excruciating detail how to do all these tests, and I really encourage you to use them because no matter what you think you've communicated to the patient, it's often not what they heard, so keep that in mind.

Mark Newman: Right.

Chris Kresser: So, Mark, you just talked about doing some additional testing to look at how DUTCH correlates with CAR. What else is on your mind in terms of future developments for Precision Analytical?

Mark Newman: There's a lot of, for us, I think, clinical application that we have yet to do. With our test you can look at methylation, so then doesn't it make sense to do an actual correlation with our actual test to genetic defects? I don't have an MTHFR defect, but I have a COMT defect, two of them, actually, homologous for the COMT defect. My methylation stinks, and I'm having trouble improving it, but you can see the correlation there on an anecdotal basis. Same thing with things like 5-alpha and 5-beta metabolism, where we're looking at DHT production, and those are things that we can look at, and we're busy really trying to clinically validate what, to this point, has been really, really encouraging when we're looking at … we've done extensive serum correlation, pretty extensive saliva correlation with whichever hormones are most relevant to do that, but then there's that next step that I think is often missed in this—whatever you want to call it—alternative medicine lab work, the clinical validation of when you can tell a nice story based on some things that are still somewhat theoretical or there are some extrapolations made. We really want to nail those down so that it's used entirely in the best way possible and not overused and extrapolated in ways that are inappropriate.

We've also begun doing cycle mapping. I was pretty discouraged when we did saliva cycle mapping against the urine and the serum. You couldn't see that ovulatory peak. You couldn't see the luteal peak in the estrogen. It's tough to do it in urine because we have to make mass spec measurements for every one of the measurements, which is a lot more difficult than the way you do the testing in saliva, but we've done that, so we've released that, and it's just terrific data, to be able to look at everything we currently look at with the DUTCH Complete with estrone and estradiol and progesterone mapped throughout the cycle. When you're looking at women with cycle issues or fertility issues, that's a nice thing to look at.

There are a number of other biomarkers that we're looking at expanding into, but the intellectual hole that you jump into when you jump into this is so much broader and deeper that that's really where we're spending a lot of our efforts, just trying to make sure that as a provider, when this is set in front of you, that you can make sense of it, so we're embedding educational videos right in the reports so both the patient and the provider can get educated on why we're measuring phase one metabolites of estrogen, 2-hydroxy, 4-hydroxy, 16-hydroxy. What do these mean? What do they not mean? There's some confusion over some of those things, and we're trying to help people understand cortisol and its metabolism when that can be something that you need to really look

carefully at to understand it. The understanding piece of it is still really evolving because it is such a complex thing, but we are looking at some different biomarkers to add into the mix, as well.

Chris Kresser: Yeah, that's great. We were a little bit involved in the beta testing for the cycle mapping, and it's really exciting to have that kind of testing available in a way that's really convenient. I had the experience of using some of the saliva tests for that in the past and just seeing some really wonky results that didn't make sense and then following those up with serum testing that didn't match at all and then doing more research and finding out that the saliva testing for some of the sex hormones just really wasn't there, as you talked about earlier in the case of estrogen. It's great to see that we'll have that kind of tool available.

For those listening, we're not going into detail about sex hormone physiology, diagnosis, and treatment in this Level One Course. We will definitely cover it in a future training. But Precision Analytical and Mark have put together some incredible educational videos on how to interpret the sex hormone testing from the comprehensive profile on their website. They also have a fantastic clinician support department that can answer questions. In the training, I've shown both the advanced adrenal panel and also the comprehensive panel. We order the comprehensive for all of our patients just because it gives so much more information, and even though I'm not going into detail on how to assess the sex hormones, there's quite a lot of information out there and on Mark's website and through his clinical support staff, so that's probably the best test for you to order, as well. You get melatonin with that. Even if you're only looking at the adrenals, I think to add melatonin onto the adrenal panel, it's ends up being not too different in terms of price.

I'm just going on memory. Correct me if I'm wrong, Mark!

Mark Newman: Yeah, it's a little bit more for the Complete, but it is more comprehensive for the adrenals, as well, and it has to do with which methods you have to use to measure which hormones. DHEA, as an example, has three markers: the DHEA-S and then the two downstream metabolites that aren't as well known, but they represent a larger fraction of the DHEA. That's etiocholanolone and androsterone. In the DUTCH Adrenal, you just get the DHEA-S, whereas in the Complete you get this fuller picture, so when you get these situations that are interesting, like when you have inflammation, inflammation blocks the sulfation, so now the DHEA-S will go down and you think, aha! You don't make DHEA! But if it's an inflammation situation, the DHEA is essentially just shifted to these other metabolites. So when you get the Complete, even if you're not ready to wrestle with estrogen metabolites and some of those, for me, it's a better picture of overall value, and you do get the melatonin, which is a nice add. Yeah, I'm such a cynic when it comes to lab testing that my first thought is always, "Yeah, really? Is that really what's going on?" So I want to see those multiple markers for DHEA, for cortisol, for estrogens, and the Complete gives you that full picture, but the DUTCH Adrenal gives you a good picture on cortisol, for sure.

Chris Kresser: Right, and as you mentioned, the comprehensive has some really pretty cool other markers for things like COMT-dependent methylation. I also have COMT mutations, and I see a lot of impaired COMT-dependent methylations on DUTCH, and that together with some other testing

that we'll be talking about in the training could be something that would spur you on to do more detailed testing for methylation, like a functional methylation profile. There's really a lot that can be learned. The other thing with the comprehensive panel that relates to HPA axis pathology is just looking at the differences in 5-alpha and 5-beta metabolism, and that can shed some light on the overall picture. It's the better test, it's the one that we order, but the advanced adrenal panel is a great test, too, so if that makes more sense for your practice at this point, either will work well.

Mark, thanks so much for your time, and thanks again for putting this test out there. It's been great working with you. As a clinician, I'm always looking for the best tools to assess my patients, and after being pretty frustrated with a lot of the other hormone testing options, it's exciting to have this available.

Mark Newman: Great. Well, we're happy to collaborate as we go forward, and as we've said over and over again, there's just so much more to learn, and when you put the lab minds together with the clinical minds, I think everybody benefits from that synergy.

Chris Kresser: Absolutely. Great. Well, have a great evening. Thanks again.