Matt: Hey, Paul, I'm excited to tell you that we are launching a Curbsiders Patreon, have you heard about this?

Paul: I did because I work with you. But tell me more about it.

Matt: All right, Paul. Well, we want to be able to keep offering this great free content and we're doing things like upgrading our website, we offer transcripts now for episodes, recording new seasons of our Miniseries Teach and Addiction Medicine. The digest is growing. And Paul, now we're on video. People could see us as we're talking right here.

Paul: What a treat for our listeners.

Matt: That's right. With Kashlak admitting privileges, they're going to get all episodes ad free. That's the whole back catalog plus future episodes. And twice monthly, there're going to be bonus episodes where me and you recap a show and answer some listener questions. So, people should sign up today at *patreon.com/curbsiders* and you get a whole lot of more of Paul, America's PCP.

First one that came up, this is from 11 Hilarious Arthritis Puns. You know, Paul, apparently there is bipartisan agreement in Congress for medical cannabis that it should be allowed for the purpose of relieving arthritis pain. You know why?

Paul: Tell me why.

Matt: In other words, Paul, there is joint support for joint support to joint support.

Paul: Ah, that's terrific.

Matt: Okay.

Paul: Yeah.

Matt: Yeah. There we go. All right.

[Disclaimer]
[The Curbsiders theme]
Matt: All right, Paul. Welcome back to the Curbsiders in person here ACP Internal Medicine 2023. This will, of course, be released after the fact. But Paul, today we're talking about wisely ordering autoantibodies, certainly a topic that I could have used and now I feel empowered. How about you?

Paul: I feel much better about being more restrictive about my ordering. There'll still be the errant ANA that I don't know what to do with, but I feel like I'm going to do better after this episode.

Matt: Yeah. And our guest, Dr. Matthew Carroll, will tell you a bit about him in a second.

But Paul, what is it that we do on Curbsiders?

Paul: Thank you for asking. We are *the* Internal Medicine Podcast. We use expert interviews to bring you clinical pearls and practice-changing knowledge. And Matt, you were about to tell us about our excellent guest and a little bit about what we talked about.

Matt: That's right. So, Dr. Carroll is a rheumatologist. He went to Uniformed Services University. He worked as a medical officer and leader in the United States Air Force. He served tours of duty in South Korea, United Kingdom, Saudi Arabia, Colorado, Kuwait, and Oman. In 2007, he completed his rheumatology fellowship and relocated to Keesler Medical Center in Mississippi. There he was a dedicated leader helping restore a residency shuttered by Hurricane Katrina.

He served as associate program director of the Internal Medicine residency, guiding the program to meet the next accreditation standards. He initiated multiple clinical trials, led the IRB, and served as the Designated Institutional Officer, the DIO. Upon retirement in 2017 from the military, he's working in Singing River Health System. He has been an ACP member since 1996, Paul. Active in the Air Force chapter. He's been part of the Board of Governors from 2002 to 2005. He's won a Chapter Laureate Award in 2021, and he served as the Air Force ACP Chapter Governor from 2017 to 2021 and received the honor of Master American College of Physicians in 2022. So, needless to say, we are thrilled to have such a great guest on this episode. A reminder that this and most episodes are available for CME Credit for all health professionals through VCU Health at *curbsiders.vcuhealth.org*. And with that, let's get on to the interview.

Matt: Audience, this is going to be our take two because I forgot to press record, so we'll do it again. Okay, Matt, thank you for answering this question twice in a row. So, welcome to the Curbsiders and give the audience a hobby or interest that you have outside of medicine.

Dr. Carroll: I like to garden. I think that's fun, that's a nice way to relieve stress. And living in South Mississippi, it's easy to almost get two seasons growing. I don't usually do successful in the fall, but I'll get some tomatoes and other veggies before the bugs get them. And then I like to run. I think running is just a good way to offload stress and stay cardiovascularly fit and try to keep the cardiologist hungry hopefully they won't be stenting me at any point soon.

And then my wife is certainly my better half. She keeps us busy. We've got young kids and we're running around taking care of them. And so, I try to do, I'm a mad scientist for my kids. They're in middle school and, well, really upper elementary. So, I was a chemist-

Matt: Oh nice.

Dr. Carroll: -it was my bachelor's. I dress up with white hair in a lab coat, and we just do

cool experiments, and the kids like that, too. So, a little bit of everything just trying to stay physically active.

Matt: It might get a YouTube channel with this.

Dr. Carroll: I thought about it. I'm not as tech-savvy. My wife's a lot smarter. She tried and we almost did that with the pandemic. But I just try to stay busy in certain activities in areas because I think, as we all know, as the kids grow up faster and life goes on, there's so much going on.

Matt: Yeah.

Paul: This touches on two things that Matt and I have talked about and that the people who garden seem to be much better adjusted than people who don't. And then also we were talking earlier about how running is more to prevent psychopathy than it is to actually make you feel good. I don't know but for me it just keeps seeming slightly homicidal.

Dr. Carroll: I assume and that it is a bit stressful. And then yeah, at least for me, gardening. You're going to be thinner. Yeah, sorry.

Matt: Gardening, still Paul. Audience eventually I will start a garden Paul same. I think-- [crosstalk]

Paul: I need a yard first for sure.

Matt: A yard is in your near future Paul with this upcoming move.

Dr. Carroll: Awesome.

Matt: I think a garden is in your future. So, Paul, do you want to ask anything?

Paul: Sure. And then you were giving us some excellent advice before we started recording. So now that we have actually started recording, I would love to hear that advice to its completion.

Dr. Carroll: Yeah, well, first of all, again, thank you for having me here. It's really an honor to be on podcasters and to just hopefully provide a very informative session for all of us here. But it's certainly more important for the listening and viewing audience. I joked about earlier, patients and other docs will come to me sometimes and say, "What wisdom do you have? What advice do you have?" And I always jokingly say, but it's partially true. "As the gray hairs are getting deeper, it seems like we're going from a 64K down to a 32K down to a smaller and smaller memory."

But the reality is, I think the takeaway is we are under a tremendous amount of stress every day as we see our patients with regard to trying to be productive for RVUs and

get that next patient in and just move people through. And that really, I think, drives us further and further from the essence of medicine, which is providing really a global, more holistic care for our patients. And I've really been focusing on the past five or 10 years and maybe if not a little bit longer on the service aspect of it. I think in medicine we're here to serve, we're here to give back to our community and build and nurture, especially in some of the turbulent times that we've seen.

I think just taking the time to know your patient. Go that extra mile for your patient. Not always easy. I mean, I certainly stumble on that journey, but it's a blessing to be able to take that one extra step and maybe get that medicine for a discount because you took the five minutes or your nurse took the five minutes to get them the medication card for the discount or to arranging for transportation or something like that, which can be a real-- it takes some time, it takes valuable time from you and all your staff.

Paul: I think probably one of the best headspace adjustments I've made in my entire career is recognizing that the goal is to get patients towards a shared health goal as opposed to getting them to do the thing that I want them to do. And once you even make that adjustment, life becomes so much better.

Matt: Yeah. Early on, I used to take it personally if the patient didn't do the things that I was trying to arrange for them and then I was like, "Oh yeah, that's because they didn't want to do them." I should probably find out what they want and then if we're working together, it'll work better and I will be less frustrated with things.

Paul: Yeah.

Dr. Carroll: Or sometimes for them.

Matt: Yes.

Dr. Carroll: Yeah.

Matt: So, I think we're in a good spot, Paul, to just jump into a case from Kashlak. Paul, would you do the honors of reading it just because I think everyone loves to hear from America's PCP.

Paul: Yeah, yeah. My soothing baritone.

We're going to talk about Jocelyn, who is a 44-year-old female. She has a history significant for chronic low back pain, migraine headaches, pure hypercholesterolemia (mild), a BMI of 29. She's coming to our primary care office for an initial visit. She's reporting joint pain in her knees and her hands. The pain has been present on and off for years, but has gotten progressively worse over the past six months. She has stiffness in her knees and hands upon awakening. She works in an Amazon warehouse packing and stacking boxes. She states her energy level could be better as is true for all of us.

Her grandmother and her aunt have arthritis, but she's not sure what type, whether or not they take any medications for it. And so, we have a picture here that I feel like it comes up all the time in primary care where is this inflammatory arthritis because she has-- Some of the things is a simple arthralgia. And I guess the question for you, Matt, is how do we tease this out and sort of what are you listening for in the history to help make that initial determination sort of guide the rest of the visit?

Dr. Carroll: I think a couple of aspects here. One, obviously there seems to be some chronicity to it. I think the case had mentioned that it was about six months in. So, at least if you look at a bunch of different guidelines, it looks like we're past six weeks for a threshold where you might want to be considering more long-term potential for an autoimmune issue. The reality is this screams fibromyalgia to some extent and there's other chronic pain syndrome that might be coming in here, but in an ideal way. If you could find some degree of synovitis or actual swelling in the joints on exam that would probably be a little bit more of a tip-off. And I think also what we don't really have in this case, but I know it's a vignette, is just some other things to think about is, is their evidence of sclerodactyly, is there evidence of Raynaud's or a history of Raynaud? Is, there excessive dry eyes, dry mouth? Is there anything else that might really steer you toward, like, ANA positive autoimmune condition, the five of those being lupus, idiopathic inflammatory myositis, Sjögren's, mixed connective tissue?

I think irrespective if you don't have any of the telltale signs for that, then it's probably worth saying, all right, look, right now it may just be that you have something like fibromyalgia, maybe any other additional screening that might be appropriate for that would be the next to consider and move on from there.

Now, if symptoms develop and change, that's where you might want to reinvestigate what's going on. And I think not to be too preachy, but a lot of us know in our day-to-day practice, medicine is an iterative process. You'll see somebody and your pretest probability is low, but then six months later, they come in with evidence of digital pitting on their fingers or maybe new dry eyes, dry mouth, just something else that then says, "Hey, I didn't capture this before, but now maybe I need to reinvestigate and go back through that." We did a pretest, here's the testing, here's the post-test, let's bring the post-test back for another pretest and keep doing that cycling.

Matt: Yeah, I guess part of the point is, I've seen patients present with new rheumatoid arthritis and they were obviously inflamed, and they could barely move, and it was really not subtle.

Dr. Carroll: Right.

Matt: Some of the other patients, it took a while for things to really declare themselves. It sounds like that's what you're getting at. And you can maybe tell by how bad the person looks in front of you.

Dr. Carroll: Exactly. And by the way, just again, gray hairs, remember, five is scleroderma, that was the one I think I missed, all right, sorry. But that aside yes, absolutely. And usually, the ones who are really more active with a lot more going on, they're going to declare themselves much earlier. It doesn't mean you can't have rheumatoid arthritis. That's really smoldering or say lupus that's smoldering over a period of time. So, that's where that iterative process of following up with the patient, seeing how you're doing, getting them back in a couple of weeks, trying a medicine that fails, maybe try the next step. And despite a lot of our advances in medicine and rheumatology, certainly, as well. We're still blessed with the follow-up aspect to get patients back and how are you doing? And have we made an improvement? Are we failing here? What's next?

Matt: Yeah.

Paul: And for someone like this who's coming in largely undifferentiated, maybe we're waiting for something to declare itself. What other historical things are you asking about specifically at this initial visit to at least get a sense of where you think things are going?

Dr. Carroll: Yeah, and I think a lot of that harkens back to what we had brought up before. So dry eyes, dry mouth, that's one that's easily overlooked. And that can be a little difficult to assess. I mean, there you might want to ask them how frequently do they use over-the-counter eyedrops. Do they have to drink frequently at night? Do they drink frequently throughout the day? That may not per se diagnose them with obviously sickest symptoms, but that might be suggestive of it certainly poor dentition as a consequence of months or years of sickest symptoms.

Sclerodactyly, Raynaud's is another big one. So, I think for a lady in this population, certainly if she's "Hey, I've had Raynaud's for five years." And now you see some sclerodactyly on your exam that's going to be like, "Hey, there's more going on here that meets the eye.

Matt: And sclerodactyly like sort of the thickening of the skin, the fingers are curled a little bit.

Dr. Carroll: Absolutely and that might be more of an advanced finding, but at least some sort of loss of skin turgor is probably the better way to put that on there or a better way to frame that. What else? Rashes? Any rash that'd be somewhat suspicious. Little challenge there is, of course, the malar rash, because a lot of times ladies in this age might have acne rosacea or if they're of darker complexity, it might be difficult to diagnose. So early acne rosacea can spare the nasolabial folds, and that's a classic for the malar rash is it should spare the nasolabial folds as compared to go over it.

That can be a challenge. But that might be a little tip off too. And I see that occasionally. That's a challenge where you get somebody with fatigue and achiness and they have what probably is acne rosacea, but is interpreted as a malar rash, and then that ANA is fired. But again, you're seeing the patient, you're trying to interpret everything that's

going on, and so I really don't try to-- it's easy to be the Monday Night Quarterback and say, "Well, it's crazy to order that ANA." But that's what you were seeing at the time. So, you go with your suspicion. And then again, you update your post-test probability to be your pretest again.

Paul: And can I ask about the physical examination? I feel silly at this point in my career asking, but synovitis, just talk me through a little bit of what you're looking for and what that feels like. I know everyone-- was some bogginess, and you're like, I just don't know what that means necessarily.

Matt: And this patient specifically was saying joint pain in the knees and hands, and maybe there's some morning stiffness. We didn't get too deep into that you know.

Dr. Carroll: Yeah, no, and that's perfect. And that's a challenge because I'll just tell you, even when I was a rheumatology fellow and we're on rounds, you know, the gray hair at the time, right the ones who taught us, they would be like, well, there's some trace synovitis. And then you're sitting there going, "What does that mean?" [Paul laughs] It's a challenge. And I guess it gets back to the old adage, you know it when you see it.

There is going to be some times where you're like, "Wow, those second and third MCPS are pretty obviously swollen and there's a degree of bogginess and just a very easy elicitation of pain when you press on it." But it's the repetition in the exam that I think will help you over time realize. Yeah, that's probably more tender than it is swollen versus obvious swelling and tenderness. But it is hard. It's a challenge even for a rheumatologist.

Matt: Bogginess.

Dr. Carroll: And I'm speaking about myself maybe, but it can be a challenge.

Matt: So, assuming I don't have rheumatoid arthritis, if I feel my own joints and then feel the patients and there's a little bit of a sponginess or give to it, then that's like sort of--

Dr. Carroll: Exactly. And you should be able to feel like between say, the metacarpal and the phalange, you should be able to feel like a little ring or an indentation and sometimes you don't get that. Now, it gets a little bit harder as we get older, of course, because if you got osteoarthritis or other types of arthritis, there might be-- well, osteoarthritis, I guess being the main one. The PIPs and DIPs may really have substantial changes to them that reflect chronic rather than acute. So, more of a chronic synovitis picture and it's tough.

Matt: And how much stock do you put in the morning stiffness question is that?

Dr. Carroll: It's a challenge because in a perfect world, less than 30 minutes, you would think that's probably your typical wear and tear. I know my fibromyalgia patients can have morning stiffness that lasts several hours. You sit there scratching your head

going, "Okay, well, they've got what would technically fall into the range of an inflammatory arthritis." And yet they really don't have anything on the exam.

So, again, that's where you're looking at the whole picture. It can be challenging and it's challenging as a rheumatologist. It can be challenging certainly as an internist and a specialist, it's hard. And I think that's that iterative process of trying to keep gathering more information and help you update of its probability.

Matt: Okay, so let's say we conclude that she has morning stiffness that never quite goes away and she doesn't have any joint deformities or active synovitis on our thorough joint exam after talking with you, we think we got it down a little bit.

Dr. Carroll: Awesome.

Matt: Let's say we even got x-rays. We don't see any erosions of the hands, the wrists, the knees yet. And we think this could maybe be early rheumatoid arthritis because she has this symmetric arthritis, it's involving the hands and she's got morning stiffness. She says maybe she has a little fatigue. What would be like your initial tests that you would order after that, like serologies?

Dr. Carroll: Well upfront, hopefully, to enter the 2010 classification criteria for RA, which again in rheumatology we use a lot more classification criteria to help us with homogeneity from a study standpoint but they can help.

Matt: By [crosstalk]. Yeah.

Dr. Carroll: Yeah, exactly. But they certainly can help us in a quasi-diagnostic sense, but they're not diagnostic, and that's a talk for another day. If you have synovitis plus the history that's observed, let's assume that's going on here. Now you're looking at an ESR, CRP that would be potentially the next to assess inflammation and get the rheumatoid factor and anti-CCP. And with the 2010 classification criteria, those are the ones that would be the next that if you're getting positives on those, either low or high amounts of inflammation or a strong or weak positive rheumatoid factor of CCP, those would start to give you certain amounts of points that might push you more toward a diagnosis of RA.

Matt: Yeah, I've heard some people say they order, like, a CBC and a CMP. I have seen elevated white count and some liver enzymes that are elevated. And I don't know if you throw urinalysis and if you're ever considering could this be arthritis or just, like, your simple osteoarthritis or is this like inflammatory arthritis? What else do you order?

Dr. Carroll: Well, if I'm thinking RA, I usually limit it to those with some of the novel markers that we'll talk about here depending on clinical suspicion. If I'm thinking more of lupus, even Sjögren's, I'm thinking more in that flavor of an autoimmune condition, urinalysis, usually I get a urine protein-creatinine ratio just to make it easy. And my lazy rheumatology ways, I guess, speaking for myself, not us as a community, I don't want to

know if there's blood in the urine. And I don't mean that in a bad way, because--

[laughter]

Matt: You don't want to get stuck with this [crosstalk]

Dr. Carroll: Hey, man, it's like you're a 65-year-old lady who you're just like, "Oh, I know that there's-- well, I'm not worried about the cysto more, just the UTI because that's one thing I should say. I don't want to know anything about a UTI. Is there protein or not? And if there's a lot of protein, that's important.

Matt: This past week, I ordered the UA and the urine protein-creatinine for a patient that I was working up for this and they had microscopic hematuria, no protein. So, I'm like, darn it, now I got to go.

Dr. Carroll: Exactly. And I'm just bringing that up on a humorous note. I mean, obviously, you get a urinalysis, and if there's blood and protein, sure you work that as appropriate. For me. I guess I've just gotten lazy in the sense that if I open the hood and I see that there's certainly, like, 2 g of proteinuria that's put me down more lupus, Sjögren's path there and then I'll get the UA and that might give me additional information about what else was coming through crenated red blood cells or something like that [crosstalk]

Matt: Good thing Dr. Paul Williams, America's PCP is working on a hematuria episode that will be coming out very soon.

Dr. Carroll: God bless him, yeah, yeah.

Paul: I feel like. Yeah, these initial tests invariably will come back with, like, an elevated sed rate, but a normal CRP, and maybe the rheumatoid factor is positive, but the CCP is negative. And you're like, "Okay, well, now what do I do with this?" Which I guess is what we're going to be talking about the entire back half of this episode.

Dr. Carroll: Now, I'm sorry to interrupt, if you don't mind really quick, Matt. So, one other thing to think about is just to answer your question. Yeah. So, there are some key opinion leaders that suggest getting a CBC in the sense that if you see an elevated white blood cell count, that might be a tipoff. So, yeah, anything that drives you? Is there inflammation? Now, again, just looking at the boundaries set up by the 2010 classification criteria for RA, since we're on that right now. There's nothing in there about a CBC or whatever, but that does give you more credence, so you've got an elevated ESR, maybe a slightly elevated CRP, but the person's got a BMI of 30 and then you have some leukocytosis. And there's no other clear reason you're like, "Mm, all right, there might be some actual inflammation here." That's not related to cystitis or steroid use or you name it. And then the Chem-7, sure that's probably not unreasonable to do. I'll do that based on what I think potentially is going to happen down the road with regard to treatments.

Matt: Okay, got it.

Paul: This kind of makes sense.

Matt: Let's give you some labs here. So, we have a mildly increased white count and CRP. The kidney and liver functions are normal, or the liver tests, sorry to my-

[laughter]

Matt: -hepatology listeners. And rheumatoid factor is positive, but CCP, which is now, I'm told, ACPA for anti-citrullinated protein antibody or peptide antibody.

Dr. Carroll: Peptide, yeah.

Matt: Anti-CCP or ACPA, you might see it, listeners. So, let's say the CCP is negative, but the rheumatoid factor is positive. Matt, what do you think about those?

Dr. Carroll: Well, let's assume again she has synovitis. At this point, if she's got true synovitis that you're like, those are definitely swollen, tender joints, and she's got at least more than 10, and she's had her symptoms for a couple of months now, obviously. And your ESR is elevated and your rheumatoid factor is elevated. I'd always have to look back at the guidelines.

Matt: Yeah.

Dr. Carroll: You're pretty much there at that point by saying, "Hey, I think you got rheumatoid arthritis." And then if you feel that's within your wheelhouse, you can certainly start treatments for that. If not, send it over to rheumatology, obviously, just saying, "Here's what I found." And yea or nay [crosstalk] so to speak, to give the thumbs up or thumbs down.

Matt: And is the cut-off for rheumatoid factor somewhere around 30?

Dr. Carroll: Sure. It depends on your lab. I think mine is like 14. What would be helpful-- rheumatoid factor, that's a talk for another day too is if you get this rheumatoid factor of 17, you're like "Ha, it's a low positive and I'm not really sure what to do there." Rheumatoid factor of 17 with a CCP of 250. Okay, that's like a slam dunk there. Rheumatoid factor of 270? Okay, well, then there's a differential that goes with maybe Hep C screening, Hep B screening. But you're probably heading in that direction if those come back negative for Sjögren's, RA, something along those lines.

Matt: Okay.

Paul: And we may have glazed over this and apologies, this is a repeat part, but I don't know if we talked about sort of your approach to imaging after this initial presentation. Is

this someone that you would get x-rays in the hands and feet or wrist right away?

Matt: We did give some X-rays. We jumped ahead of that just to-- I guess the way that the case was written was just to take that off the table. But yeah, when would you get those? Would you get those after or before the?

Paul: That was my question. Yeah.

Dr. Carroll: I usually get them up front in part because if you get some of that ambiguity and you see some evidence of interstitial lung disease on chest x-ray, obviously not the best tool for that. But if you do that will be kind of saying, "Hey, you got somebody who's got all these serologic findings, this historical stuff, and they've got interstitial lung disease, hmm, all right this is starting to get a little suspicious." And this may not happen per se within 6 to 12 months. But let's say you get hand x-rays at the start of this appointment and you find there are actual erosions involving the MCPs or PIPs, these periarticular erosions. You're there. I mean, essentially that might be erosions, a positive rheumatoid factor, an ESR, all these clinical symptoms like that starting to pull you in there.

Matt: My understanding is the erosions are a later finding, like if you're catching someone with early rheumatoid, you might not see those.

Dr. Carroll: Exactly right. And that may be a distinction we'll talk about here, is whether or not to get MRI. I don't want to get the cart before the horse, I guess, but yeah, absolutely. So, you would hope and the aspiration that we have as rheumatologists is to capture them early. And actually, a lot of great interesting stuff now, trying to get people in the pre-RA phase. Capture them early, treat them aggressively, and never let those erosions come off, like we never want to have hand damage.

The stuff that I trained with in the late 90s was you were guaranteed to go to just severe deformities and joint replacements. That error should never hopefully happen and it remains a challenge now as a rheumatologist, because I'll get patients come in and I'm like, I don't really know. Do you really have RA? Well, then probably I'll repeat a CCP, okay, It's positive. The whole idea is we really want to keep people in remission and control and never let those erosions develop, and never let the lung stuff come up, never go down that road.

Matt: And this is one of the diseases where once you have it under control, you keep your foot on the throat of the disease. You don't just say, "Let's see how you do off your medication."

Dr. Carroll: Exactly. And I tell patients, "We don't know how to hit-," and this is an 80s reference here, "-the eject button from the cassette player just yet. [crosstalk] But we know how to hit pause."

Matt: We're kids of the 80s.

Dr. Carroll: Awesome. We're birds of feather that's good. So, I know how to hit the pause button. I don't know how to hit eject. But there's very smart people trying to figure out how to hit the eject.

Matt: Yeah.

Dr. Carroll: And maybe one day we'll be there.

Matt: Yeah. So, in this case, we gave-- she didn't have synovitis by our exam, but I probably would send this patient because she's got enough features, a positive rheumatoid factor. I probably would send her to you to see what you think. And maybe she is someone that's early. Maybe she's someone we caught. But this person has, one, she has a positive rheumatoid factor, no synovitis, the CCP was negative. What else can we do that might help us figure out? And what's the new stuff, the fancy stuff? Because our listeners like to be well informed, Paul, right they want to show off.

Paul: The leading edge of the blade. That's right.

Dr. Carroll: The tip of the spear, as we say in the [crosstalk] Air Force, yeah.

Matt: So, what's the new stuff that Paul and I will try to remember of these autoantibodies?

Hey, everybody, this is Watto. I just wanted to break in here and set up this next section. We're going to talk about. Two newer tests that you might think about ordering for patients with suspected rheumatoid arthritis. As we get into, these can help you pick up some extra cases, who are missed by the rheumatoid factor or the CCP testing respectively. So, these are 14-3-3eta protein that's an inflammatory marker of sorts that you can send. And then finally, the second one is the anti-CarP antibodies. That's anti-carbamylated proteins is what it stands for. And those can pick up another maybe 10% or 15% of patients that you might miss with the more traditional testing for RA. So, with that I just wanted to set up this next segment and let's get back to the show.

Dr. Carroll: Well, there's actually several, so I'm going to cover just two because there's another thing called anti-Sa antibody that's really been around for-- it's old, but it's new. It's citrullinated vimentin. I talk, but I think, beyond this, but what I'm presenting here at the conference are two additional RA labs. One is what's called a 14-3-3eta protein. And I believe that got its name because of the way it patterned out on gel electrophoresis. The name is really annoying, I guess, but the reality is it's an ISO form. There's actually six or seven of them these proteins that like to dimerize. It's the 6th of 7th, and it's unique to brain and to synovium.

Now, let me step back for a second. I guess I'm getting again the cart before the horse. As the trends in rheumatology have gone for RA, we're trying to take the needle from the 90s, when it was established disease, to the 2010s early disease, to now pre-RA.

So, in that process, when you look at the RF and CCP specifically for established RA, you're missing about 12% of patients with the RFs and CCPs. With the Rheumatoid factor in CCP for early, you're missing about 28%.

So, there's a big gap there. And the whole idea, like I told you earlier, is we want to capture this very early. We never want erosions; we never want deformities. We don't want any of that at all. So, these other labs might be helpful. Back on track. 14-3-3eta is really an inflammatory marker, and so it's not an antibody. So that's like an adjunct, maybe if you want to think of it as in the same family as the ESR and CRP.

Matt: Okay.

Dr. Carroll: And so, a value of 0.2 ng/mL or higher is considered positive. I will say when it's the 0.2, 0.3, 0 4, I'm like, "Ha, what does that mean?" Now, if they're 0.4 and they've got a rheumatoid factor of like 230, I think we're there. If there is more of an OA picture with 0.4, I'm like, "Ha, I think we'll just watch them wait. I wouldn't diagnose it based solely on that." But the strength of that test comes in conjunction with other antibodies that you might have. And we do think that when your rheumatoid factor and/or CCP and/or both positive, that adds another 15% that you're going to capture if that protein is positive too.

Matt: Okay.

Dr. Carroll: 0.8 or higher is what really sets that you like you're there and you've got an abnormal test. And again, I wouldn't diagnose RA alone just based on that. And again, that's staying within the 2010 classification criteria. But that can, again, be of help to you there.

Matt: Did you mean if the CCP and the rheumatoid factor are negative, but you're still suspicious and the 14-3-3eta is positive, then that might capture extra people?

Dr. Carroll: Absolutely. That's all I did, is we're trying to capture extra-- Yeah, I'm sorry, that's why I give that and/or, and/or kind of thing. Yeah, so you're going to probably capture about 15% more people in that scenario there with that 14-3-3eta protein and earlier disease too, which is nice because you'll capture them early.

Paul: Where it actually matters.

Matt: This seems like this would be a send-out lab that-- I don't know, I haven't tried to order it, maybe now I'll look into it.

Dr. Carroll: I know for me, initially, it was, let's see, so rolled out in the mid-2010s. Working with the lab, they were pretty straightforward. I think it should be relatively easy if you work with your lab department to get that squared away.

Matt: Okay.

Dr. Carroll: It's been around for almost about 8 to 10 years now or 7 to 10 years. [crosstalk]

Matt: All right. I'm just late to hear about it.

Dr. Carroll: Well, I think we're still back a couple of years ago, it was a little bit more half-baked, and now we're getting to the near completion of it.

Matt: Yeah.

Dr. Carroll: So, if you're in the baking process I think

Matt: Sort of figuring out where to use it. Okay.

Dr. Carroll: Exactly. You got to have a lot more studies roll up. And then on the CarP, so CarP stands for carbamylation. But when you look at the likelihood ratio for the CarP, I think it's about one or somewhere in there, it's really not as good. So, with the CarP, if that's positive and everything else is negative, you might capture another 5% to 10% of patients with it. And my caution there is, again, we're not in the same arena as the 2010 classification criteria with these.

A positive CarP and not a really convincing exam, it might be like something you want to watch or wait. This is the way I would take it as a rheumatologist. I think as an internist, if you were to get that test, I don't know what to make of this boom, send it over to the rheumatology, and let us figure it out.

The reality is, "I would probably watch and wait for somebody." But if you're RF positive at 100 and you've got anti-CarP that is like 40 units or whatever, that's a positive test. I think anything over 20 or 25, then you're there. I think at that point, you'd probably say, "Look, with the elevated ESR, the leukocytosis, your clinical history, and these other autoantibodies were probably there. Just the key takeaway is that the two of them, one, they're not within the confines of the current classification criteria. But they can still clinically educate us. And then two, the CarP, I don't think really has the strength that the 14-3-3 has and those are still not as good as the CCP.

Matt: Yeah. I wonder if these will be incorporated in future guidelines or just when this is written about in the future, there will be more guidance on how to use these so we can make that earlier pre-RA diagnosis and use that to treat people early to prevent any joint deformity from happening.

Dr. Carroll: Yeah. I don't know where that is in the process. I wouldn't be surprised if they're-- I mean, 2010 has been a while, but I still think those criteria are serving us well. I don't know how they're going to incorporate a lot of this new stuff. And there are still more antibodies beyond it, but those are the two more mainstream ones, I think, that are out there.

Paul: Yeah. Given that I don't know what to do with the RF half the time, I think I'll probably leave it to my friendly neighborhood rheumatologist, but it's good to know that they exist.

Matt: Well, let's just say that to round out our first case, Jocelyn, this was our 44-year-old female with the knee and hand pain. Let's say that we actually sent her to you. We thought she did have early RA and she was started on treatment. So happy ending for her. But let's go to another case, I think maybe the tougher of the two in some ways. So, Paul, do you want to read this one?

Paul: Sure. We're going to now be talking about Sharon who is a 33-year-old female. She has a history of rosacea, obesity with a BMI of 34, and low back pain. This should sound hauntingly familiar. She recently saw dermatology for hair loss. Her iron indices and thyroid testing were normal, but an ANA was positive at 1:80 with a speckled pattern. She's had Raynaud's phenomenon since she was a teenager. No cardiopulmonary complaints. She does not have dry eyes or a dry mouth because we took a great history. No exam, she does not have synovitis, and as much as we can tell, she does not have sclerodactyly. There is no objective muscle weakness. She does have mild erythema of the chin, the cheeks, and the nose, which include the nasolabial folds.

So, Sharon is coming to us with this now, the abnormal lab is really the thing that we're going to focus on, at least to start, of this abnormal ANA. And I think everyone at this table has probably been guilty. We won't include you Matt Watto, I think we've probably at least checked one ANA that's come back sort of vaguely positive. We're like, "Oh no, now what?"

Matt: Yes.

Paul: So, I guess for you, what are we to do with this information and how would you explain it to the patient when she's coming to us? Like, I've got some abnormal labs. Does this mean I have lupus? What do we do with this?

Dr. Carroll: No. And that's really good. One last thought about this case we just talked about, too. As you see your friendly neighborhood rheumatologist doing some more of these tests, you'll eventually get that pickup into your practice, imprint on you about where to go? So, for this case, I think as a rheumatologist, and I think you would hopefully feel comfortable doing this as an internist, but I get that. I mean, it can be challenging as an internist medicine so broad and deep in many areas. You're really done with her. I don't think there's any other testing that would need to be done. You got a 1:80 speckled pattern that's probably just reflective that she's a lady and a human on planet Earth and you're going to have a positive ANA at 1:80 and probably about 20%, 15% of ladies that high. It's even higher for a 1:40 and less for a 1:60. And the pattern is kind of insightful but not very specific at this point.

And you really have a history and a physical that seem to go with some other alternative diagnosis. So, you really at this point could pump the brakes and say, "Look, yeah, I know you've got that but I'm not really convinced that's meaningful for where your disease is at this process, if anything new develops and maybe it's worth repeating that down the road as clinically guided."

Matt: Yeah.

Dr. Carroll: I'm not saying to follow sequential ANAs because sometimes the primary care docs will do that or our allied health professionals and you'll get this up and down in the ANA, which is not really helpful either. Just again, that iterative process of "Okay, we did this at time point A and this is what we were thinking at the time, but now we're B, 3, 6, 12 months down the road and there're new clinical symptoms. Then that's time to go back and maybe re-update what you're doing test-wise. But I think here you could potentially stop. And I think the questions will go on. We'll talk about the differences in the testing because that's certainly one place that-- ANA testing is really unfortunately not very easy because of several different things and automation a few of the things we'll talk about.

Matt: Because when you look at the workup for hair loss, which we talked about this on the show before, if it's nonscarring hair loss, to me the ANA doesn't really have a role unless there's a lot of other features where you think lupus might be part of it. And I've seen several patients get an ANA sent and it comes back like this. That was my impetus to put this case here. And then the rosacea thing too. You talked about a little bit early on that lupus commonly spares the nasolabial folds, but rosacea can do that as well.

Dr. Carroll: Early.

Matt: So, how do you differentiate between those two? I read that maybe if the person has a lot of inflammatory symptoms of the eyes as well, that's more of a rosacea thing than a lupus thing. But I'm not sure what else you find helpful with the malar rash question.

Dr. Carroll: Time.

Matt: Time. Okay.

Dr. Carroll: Yeah, just that iterative process again of watching your patient how they're doing and getting them back in a couple of months. Maybe trying on some acne rosacea therapy if you feel comfortable with that maybe, getting [crosstalk] sense on it, whatever I think floats your comfort level and the busyness of your practice. It's easy to say, well, you should do everything, and that's not the case. It just what you feel comfortable with or what you feel. So, I think here I'd give it more the tincture of time rather than trying to just over-diagnose something that may not be there.

Matt: And I've now seen, I think, two patients who developed-- they were in the hospital

with acute lupus, and I saw the malar rash come out over hours, certainly over days, and to me that was just very striking. I'm not sure if that's classic for it or if they can have this chronic malar rash that just doesn't go away or it's there for weeks.

Dr. Carroll: For your systemic lupus erythematosus or your SLE that can be very acute. That's a very quick on-and-off rash.

Matt: Okay.

Dr. Carroll: Some of my subacute cutaneous lupus and then certainly more for my chronic cutaneous lupus, you can get this chronic malar rash that just- [crosstalk]

Matt: So, then it would be.

Dr. Carroll: - cosmetically. Yeah. So, you have a chronic malar rash? Yeah. That certainly seems to suggest that you're falling more in the chronic cutaneous lupus, which, interestingly enough, only about 10% of patients actually have systemic lupus with it. So, malar rash, 90% of them likely have lupus. Like, at that point, you're there again, like with what you described, you're more the chronic that's still lupus-like skin lupus. And it's confusing, but it's really less likely to be global lupus or systemic lupus erythematosus.

Matt: Okay, cool. Paul, you looked like you had a question in there. I might have talked over.

Paul: No, no. You're great. No, more I thought I was going to say, and we might be jumping ahead a little bit here, most of the ANAs, I'm very good at blaming myself and feeling guilty about things, but most of the randomly positive ANAs I've seen have been part of order sets. So, if someone has an acute kidney injury or if someone has an acute liver injury or something along those lines, it's one of the battery of tests that you just sort of click a bunch of buttons and then it comes back vaguely positive and you're like, "Oh, no, now what? Where to go from here, I guess, is, do you have a differential for a patient who just has a positive ANA and nothing else or is it just a matter of one of those things? How do you think about that broadly?

Dr. Carroll: Yeah, so two things real quick. One, there's always been a part of me that leans and maybe I don't know if it's because now I'm a specialist. I think if you're dealing with visceral organ involvement and I'm going to speak for myself and this is not per se global guidance from key opinion leaders, and I don't consider myself a key opinion leader. So, somebody comes in with proteinuria, checking ANA there is probably not unreasonable because you want to make sure. I've had two or three cases throughout the years, where they are pretty much just lupus nephritis and there's nothing else going on. So severe pleurisy, interstitial lung disease, like those are probably the cases where for me and my tiny brain again is the gray hairs. Keep digging deeper.

If you're starting to destroy organs, probably not bad as a specialist to maybe consider

checking it. I think though the pitfall as you very astutely bring up Paul is that you might get this ANA of 1:80 speckled pattern. Then you're like, "Well, what does that mean?" And again, rheumatology can help you there, but that's neither here nor there. I think the bigger takeaway probably for our listening audience is, the ANA testing has evolved over the years as technology has evolved and there're really two different flavors and it's important for you to know which one you're dealing with to give you further insight. The first is the indirect immunofluorescence. And there you've got a cell that's lining a slide and it's usually what's called a human epithelial cell. You wash the patient's blood over it, you tag whatever antibodies hang behind after you've washed it and then there's a fluorescein molecule that lights up and essentially now there's a technician looking at that slide saying that's a speckled pattern and based on the dilutions of 1:80. So, this case seems to obviously suggest that they did an indirect immunofluorescence or IIF.

In the mid to late 2000s and more, so that you might find is you'll get to these what are called solid phase assays and those are similar concepts in the sense that you have a bead or you've got a plate or a well and there's some sort of antigen. So, it's an autoantigen that you would have at the bottom of that either recombinant, purified, you name it, however, they put it in there, it's attached the-- well, same thing put the blood in there, label it with another immunoglobin, and used to be enzymatic, now it's a lot more color-based and lasers, and a bunch of stuff to capture that data much quicker than just looking at color changes.

But the concept is that there's some sort of antibody against sticking to that. Those are quicker to do, but they enhance the specificity, but they really forfeit a little bit of sensitivity. Indirect immunofluorescence gives you more sensitivity but not the specificity. I'm trying to understand between which of those your lab is getting will probably help you down the road. Again, I think the easy way is if you're getting a titer and a pattern most likely going to be indirect immunofluorescence.

And at that point, you're like, I know it's going to pick up stuff, but it doesn't really help me rule in disease. And so, that's why I think here you can pump the brakes and say, okay, it was 1:80, 1:640 speckled pattern, okay, different story, maybe at that point, now you need to start getting some of the extractable nuclear antigen like DNA and a Smith and all the other ones that make up the alphabet soup of rheumatology.

Matt: Yeah. Sometimes there's the reflex. You can order an ANA with reflex to the extractable nuclear antigens.

Paul: Is there an absolute titer value that raises your eyebrows? I know this is probably not a fair question to ask. Like, you 1:80, 1:40. You can be like, especially if there's nothing else going on here, but is there just a number in and of itself where you're like, "Okay, this is probably significant."

Dr. Carroll: It's four shades of gray. I think as you hit 1:320, you're like, "Mm, okay, something's going on there." And then 1:640 or higher, but I've seen that also with patients who have Hashimoto's. And so, you do a big old workup, you find out the DNA

is negative, Smith's negative, everything else is negative. As part of that workup, we'll get somebody 1:640, ANA speckled pattern, some other pattern, and you do the rest of the workup with the auto with the extractable nuclear antigens, and you find out all that's negative. And it turns out they have actually Hashimoto's.

I think the higher the number, is certainly the more serial dilutions that you need. Obviously, the higher the titer, a little bit more important that is suggestive of, but it may not always go with a rheumatological autoimmune illness. It could be, again, thyroid or hepatitis or something different and actually--

Paul: Something's maybe going on, but not necessarily [crosstalk].

Dr. Carroll: Keep your differentials broad.

Paul: Sure.

Matt: Yeah. And you mentioned earlier the diseases that commonly have a positive ANA and you said there's about five of them. So, I just wanted to recap it. I'm trying to find them. I know I had it out here--

Dr. Carroll: I think the gray hair is receded. So, scleroderma, Sjögren's, my professors may have-- all right mixed connective tissue, lupus, idiopathic inflammatory myositis.

Matt: Yeah.

Dr. Carroll: Holy cow. All right, good.

Matt: Okay. Yeah. And lupus can be drug-induced or the systemic type.

Dr. Carroll: Yeah, more systemic. But lupus can certainly get a positive ANA.

Matt: I've never made the diagnosis of mixed connective tissue disease. Usually, that seems like that's a rheumatologist like you send them there where they've got some other that's like a little bit of what,-

Dr. Carroll: It is, it is a buffet, you get a little mix of everything.

Matt: -is it usually scleroderma lupus? Like Sjögren's?

Dr. Carroll: Usually high titer ANA with a strong positive anti-RNP or U1 RNP.

Matt: Okay.

Dr. Carroll: And then there, you've got a little like yeah, there's smorgasbord of some sclerodactyly and maybe some myositis and maybe a little interstitial lung disease.

Matt: Okay.

Dr. Carroll: Well, that sounds like that's mixing connective tissue.

Matt: And your slides had I thought this was helpful. So positive ANA, but no rheumatologic disease would be maybe autoimmune hepatitis, autoimmune thyroid disease, PBC, idiopathic pulmonary hypertension, and multiple sclerosis. So those are some things you could think about that would have that.

Dr. Carroll: Right, exactly.

Matt: I think I've actually seen recently since I've seen a patient with Hashimoto's that was really not yet treated and new and they had a high positive ANA. And I wonder if that's what it was from. I think they were still seeing rheumatology to sort it out, but that seems like that could have been it. Okay, so this is helpful. So, the positive ANA, 1:80 is like mm, but it depends on what else is going on clinically, like most of what we've talked about so far."

Dr. Carroll: I meant to bring up earlier, one of the few patterns that really may be a little bit more telltales if you're getting an anti-centromere pattern. Let's say you get a 1:640 for the titer and anti-centromere pattern, and especially if you have some evidence of, like, if you have sclerodactyly, you're there. But let's say they've got a history of Raynaud's with maybe some digital infarcts or something else strange. Then you're like, "Yeah, that's strange, things are afoot at that point." And again, any questions? "Hey, how can we help you? What's going on here?"

Matt: Yeah. And that's the limited form of scleroderma that is associated with that. Okay, so we've given our differential diagnosis for the ANA, both the non-rheumatologic causes and the rheumatologic causes. We talked a little bit about how there's the immunofluorescent version. That's where you get the titer and the pattern and then there's the newer ones, which could be molecular or enzyme linked.

Dr. Carroll: Yeah, they've got a whole bunch of those. There're many different flavors of that.

Matt: Okay, so I think we talked a little bit about what to do now when this person comes to you that had an ANA that you're not really convinced they have any rheumatologic disease going on. You said you can sort of let time be the arbiter to steal a phrase from our friend Elliot Tapper. So basically, you can wait to see if anything else declares itself. Paul, how do you handle this? Or do you have any other questions about this area before we move on a little bit?

Paul: No, I would probably handle it exactly. Surprisingly, actually, like the case where I would tell the patient, I'm not sure I would have checked this in the first place. I don't think there's anything to worry about here. And we can just sort of watch things for right now is probably how I would leave things be.

Matt: And it seems like Raynaud's is pretty common and you can have Raynaud's, I know. My wife gets Raynaud's and she doesn't have lupus, so it just depends. And how do you talk to somebody so they have the positive ANA just with Raynaud's in general? Is there anything that heightens your concern about that condition?

Dr. Carroll: Well, again, gets back to a lot of the history and physical exam. So, let's say you have Raynaud's and sclerodactyly or some evidence of loss of skin turgor distal to the MCP joints right. That's going to be a tip-off of like, "Hey, there's probably a little bit more happening here." Digital infarcts pitting, loss of pulp at the end of the fingertips. What else? Dry eyes, dry mouth might be another tip-off or maybe Sjögren's. It gets back to a lot of the history and physical about what else might be out there.

For us and for those in the audience who might be skilled at doing it, nailfold capillaroscopy can be very helpful. If you take a look at the nailfold capillaries and usually, I get a DermLite and try to take a look at with one of the DermLite things the old school way, was taking some oil immersion that you used to use for the slides and taking an ophthalmoscope to try to use that to help highlight the capillaries.

Matt: Oh, interesting.

[crosstalk]

Dr. Carroll: Yeah, that's really old school. I think if anything, DermLite makes it a lot easier and you have to get people's hands messy, I guess, for whatever that's worth. Abnormal changes there, that can be a little problematic, I think. I'm trying to think of this as an internist. That might be a little problematic if you're not doing that all the time. And to be honest with you, the busyness in my clinic, I'm not really routinely doing it unless I have a high suspicion I'll go run back and grab my DermLite.

Matt: Okay.

Dr. Carroll: I think that would be another tip-off, but another high positive ANA. I think if you've got somebody who has Raynaud's symptoms and a strong positive ANA that may not per se relate to something from a systemic autoimmune standpoint, that they might have Hashimoto's or whatever, but that might give you a little bit more of, "Hey, there could be something more happening here and maybe worth further investigating." Again, I think it gets back to your Raynaud's with the strong positive ANA, say, 1:1280, but there's really no sclerodactyly, there's nothing else going on.

You may be going, "Okay, well, these might be two different processes and maybe the Raynaud's is just by itself, but the ANA is due to something different." And I think it's clinically driven. You might go, "Okay, well, you've got scarring alopecia, you've got dry eyes, dry mouth, you've got whatever, that might steer you more toward extractable nuclear antigen or your TSH was 12. Hopefully, maybe now it's time for us to get-- maybe you're there, you have Hashimoto's or something.

Matt: So, we probably wouldn't be shot gunning the-- if we're ordering ANA, it should be done, I guess, to summarize what my take home is, and Paul, I'd love to hear if you have anything to add to this take home is, try to recognize? Do they fit into any of these buckets or do they have features of multiple things in which case I think mixed connective tissue disease, but that would make me want to get ANA. Is there a diagnosis here that the ANA might help us sort of support, like be further evidence that that's what might be going on here? Don't just order the ANA for the patient that says, I have fatigue. In that case, it may not be helpful. And there's either a reflex or maybe a second-round test could be where you get all these ENAs. Is it extractable nuclear antigens or antibodies? I don't know. And the [crosstalk] antigens.

Dr. Carroll: Antigens might be-- as you're looking for anti-smith, anti-Ro, anti-La, anti whatever, yeah.

Matt: Right. So, that would sort of be your second round of tests once you have a positive ANA and everything, you don't have to send those from the start, which I think a lot of people sometimes do, maybe because they come in a panel or something.

Paul: I do actually sometimes because I try to adjust my thinking a little bit. And I'd love to hear your thoughts on this as to actually having a differential diagnosis. I think to your point, I think we sometimes fall into the trap of this feels roomy, so you just do the ANA and then it comes back to sort of weird. So, I think this sounds like lupus. So, I might check like ANA and a double-stranded DNA. I prefer to have a differential in mind rather than just sort of checking for "something rheumatologic." Because I think that's where I've got myself into trouble with sort of nonspecific tests and then a nonspecific differential.

Matt: Yeah.

Dr. Carroll: But these are great thoughts. And if I interject, I don't want to dissuade anybody in the audience listening to this from doing what they think is clinically relevant. So, if that's in your differential and you're pretty strongly convinced that it could be there, then go ahead and get it. But it's always, I guess, the key at the end of the day, and which I hope this certainly podcast does, and maybe the lecture here and any other articles that come out in the future just in, say annals, it's an iterative process and know why you're getting the test right.

And I know we talked a little bit about the indirect immunofluorescence and the solid phase assays, and I don't think even-- it's important to know what test you're doing. But it all gets back to the test right, if the test has inherent limitations that's going to limit what you're going to take away from it.

But there's a little bit of time that can be built into some of this. I never want us to miss somebody who we could have caught earlier. I think the current switch is flipped the other way, that ANAs are just, and I think it's less internist, and I'm not trying to point

fingers. There're a lot of ANAs being ordered, and people really don't know why they're doing it and just cool to pump the brakes. What's the differential here? Lupus is really low. Okay, ANAs is probably not needed or ANA was 1:40. We're like done. I think at this point we can move along.

Matt: Yeah. And just for the audience, as a note, when we were saying idiopathic inflammatory myopathies or myositis, it used to be called polymyositis, and now it's recognizing it's a bunch of different things.

Dr. Carroll: Yeah, yeah. It's several different flavors-- [crosstalk].

Matt: We did an episode on that so they could refer back to last summer 2022. We did an idiopathic inflammatory myopathy/myositis episode. So, you can go back to that. I think we should be wrapping up here. So probably this is a great time to ask you for some take-home points. I know you just gave us some great take-home points, but from the overall episode, we talked about the patient with possible rheumatoid arthritis, and then we talked about the patient with a positive ANA, what maybe one or two take-home points on those topics?

Dr. Carroll: Yeah. So, one, it's always your pretest for suspicion, and your pretest suspicion is always updated by your history, your physical, and any other data that you're gathering. And it may be that even with some scant labs that you do like, "Hey, this person just seems like maybe they have inflammation we get an ESR, CRP and a CBC, and they all show some degree of inflammation, which may or may not be related to BMI or something different.

All right, well, maybe now it is time to check a rheumatoid factor or CCP, depending on what I'm seeing or hearing, or call them back in and reexamine them because exams are dynamic quite obviously. And then, of course, that's the global point of how you want to keep updating your pretest probability for your future to test to help you get that diagnosis. But then, of course, knowing the strengths and weaknesses of the test is always key.

And I don't think as an intern or even a subspecialist, you have to know all the nitty gritty details about indirect immunofluorescence versus solid phase assays, because to be honest with you, as rheumatologists, I understand some of that, but at a very cursory high level, it does not delve into the weeds. It's just what's my lab getting back to me as a result. And what are some of those strengths and weaknesses from a global perspective?

My solid phase assays are going to bring up a lot more information as compared to maybe the indirect. And then you might figure out over time that your practice, you might want to have some degree of, lot of labs are now going to this reflex that if the ANA is positive over a certain threshold, it will screen for the other extractable nuclear antigens to help you. I think it's the essence of medicine is we treat our patients, we don't treat numbers, we don't treat antibodies, they're there to help us, but we treat our patients.

Matt: Paul and I lament about this a lot of the time, just give me a black-and-white answer-

[laughter]

Paul: Give me an answer, just tell me yes or no.

Matt: -tell me yes or no. What should I do? But it's never that easy. That's why internal medicine is interesting and I guess that keeps us all in job. So, thank you so much for all your time today. You're presenting so much at this meeting. You still said yes to this interview, so thank you.

[music]

Dr. Carroll: Oh, that was awesome. A great opportunity. Thank you.

Matt: Lots of people are going to hear this and find it helpful, so we can't thank you enough.

Paul: Well, this has been another episode of the Curbsiders, bringing you a little knowledge food for your brain hole.

Matt: Yummy.

Paul: Great. Still hungry for more? Join our Patreon and get all of our episodes ad-free, plus twice-monthly bonus episodes at *patreon.com/curbsiders*. You can find show notes at *thecurbsiders.com* and while you're there sign up for our mailing list to get our weekly show notes in your inbox, includes our Curbsiders Digest, which recaps the latest practice-changing articles, guidelines, and news in Internal Medicine.

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Paul: And Matt, as always, I remain Dr. Paul Nelson Williams. Thank you and goodbye.

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