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An Introduction to EDS, HSD, and Genetic Testing

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Video https://youtu.be/MQe5Mjzdd6s

[00:00:00]

[00:00:06] *["EDS 101" begins]*

[00:00:12] **Dr. Brad Tinkle**:

Well...welcome! I think I started these conferences in 2006, so they've definitely grown, and it's great to see how well they've grown over the years. A little addition to what Lara said, I actually am at Peyton Manning Jones Hospital, which is in Indianapolis. I'll have to get you an updated CV.

[inaudible]

Sorry, how do I advance? The green.

[00:00:48] It was hidden by the paper. Alright. I do have a few disclosures part of you heard about, just because I'm sort of getting used to how always having to disclose anything that I do outside of dealing with EDS.

[00:01:04] As Lara mentioned, the new classification of EDS that happened in 2017 had changed a lot of things, but more abo—how we thought about things, not necessarily there's real substance behind that.

[00:01:22] And so this is a, a common table that you might see, that talks about the 13 different types that were, that were delineated in that particular classification, and if I could take a little privilege to say that there are some types, sub-types, from that, due to different molecular or genetic defects. For example, classical EDS. Typically, we've always thought prior to 2017, related to type V collagen, but in the current classification, we've included this rare type I collagen, that has a lot of classic EDS features. So, the, the new nosology, how we looked at those things, was kind of really put together more of the clinical presentation, the physical and medical features, and less so about the genetics or the biology behind things. And this is something that's readily available through the website and, and other, other places.

[00:02:23] So, one of the, one of the questions that I was very keen upon was, "What is EDS?" You know, once a label kind of got stuck with things, we kind of continued to run with it, but we needed to define what we consider EDS, and so some of the commonalities are probably obvious to you: joint hypermobility, skin features. We're talking about a connective tissue disorder. It probably involves collagen, but for like the hypermobile form, we don't really know. For many those other types, if I go back, yeah, some of these are structural collagens – collagens that make up different structures – but a lot of these genes have some effect on collagen, but not necessarily collagen themselves.

[00:03:18] Most you are familiar with the Beighton scoring system. What we did in 2017, is tried to refine this a little bit better, because as we got together in conferences like this, and the professional conferences, we started talking about, "Well how do you do it?" and "How do you do it?" and find out we all did it differently, so we weren't surprised sometimes if we had different answers. So, with the help of some dedicated people, we set, and looked, and tried to unify how we do this. It's listed here. You guys are probably pretty familiar with the pinkie, the thumb, elbows, knees, and forward flexion.

[00:03:57] But one thing we also wanted to do was – I tell everybody I do joint measurements by gestalt. That means I look at it, I determine whether or not I think it meets the measurement criteria, and there's that imprecise "yes." A goniometer is better. I have challenged myself under a couple

studies, to compare myself to the goniometer, and I feel freely confident, but I also know that there are a lot of people who have been labeled with joint hypermobility that get different opinions from different people. Especially if we're doing the gestalt, because that's some bias, whoever is doing it. If we get out a goniometer, it should be uniform. So, we should be able to actually uniformly measure how we do the exam, not only how it's done, but to the degree it's, which is done.

One of the other things that came out, was looking at what do we consider generalized joint hypermobility. How many joints need to be involved? We still have a lot of questions and that's one of the things ED Society has definitely put forth, that there will be continuing to look at all these parameters and trying to improve things, and so, we do know that people are more flexible when they're born and you get less flexible as you get older. And so, there's a point where that score needs to slide, but do we have the right points? Do we have the right number for different age groups, or for children versus adults, for younger adults versus older adults – so, there's still questions to remain, but you know, we're trying to be at least more precise of how we're communicating and how we're talking about the EDS population.

[00:05:52] The prevalence is something that bothers a lot of people, because when we measure joint hypermobility, depending on different studies, you can see a different number. This isn't just people with EDS, this is people in the general population. So, how many people are flexible? And so, that depends on the study. It depends sometimes on: Did you use the goniometer? Did you use the gestalt? Because you could be wrong. Did you look at children like pre-pubertal children? Post-pubertal children? Do you look at children at different ethnicities and races? Did you look at male, male children? Female children? Adults? Children? So, the numbers varied across a lot of different spectrums and we still need to understand this a lot better as well, and so you can see from just a few descriptors I have up, the description of what is considered hypermobile in different populations varies extremely, and that is a concern for us to be aware of. I'm not sure how we can incorporate that in all aspects of it, but it's one of the criticisms sometimes that we get for EDS was, if 60% of people have joint hypermobility – that's Korean school children – then if they don't have any problems, how do we link joint hypermobility with some of these other problems? And so definitely the studies that's being looked into and etc. is supposed to help us delineate some of that stuff, but joint

hypermobility is a key, but again it's not just as...

[We apologize for technical difficulties here]

[00:07:41] ...because there's a connective tissue. So that's where that kind of concept kind of came from and I'll introduce that simply because it will be talked about in the next talk.

[00:07:54] So, the other commonalities we wanted to look at, is – it's not – if you look at the old descriptions of EDS, it mostly talked about joints and skin, and so, we definitely need to highlight that there are certain characteristics about the skin that makes it common of EDS. Unlike joint hypermobility, here most of the EDS types have some level of hypermobility, the skin features among different types can vary quite a bit and it could be very stretchy. I'm sure you've seen people with classical EDS pull their skin up. A lot of you with hypermobile EDS, probably were told you didn't have EDS, because you couldn't pull your skin over your face.

[Laughter]

[00:08:39] The easy bruising, I'm sure most of you have that, and talk about that, and it may be the subject of a lot of different conversations: "What happened to you? Who's doing something to you?" The softer, doughy texture, there are some people who have it, others don't. When you feel it, you know it's just different. The thin, veiny appearance could be something consistent with another type of EDS. The fragile skin, the skin that wounds very easily. A lot of these are degrees, because amongst different EDS types, we will see a lot of the skin features overlapping, but it's like, which is sort of the major predominance of that skin feature.

[00:09:26] So, there's Gary "Stretch." He likes to perform. He is one that will pull his skin up over his eyes. He makes a nice turtleneck...

[Laughter]

... and so, there are people who can very much demonstrate that.

[00:09:42] This is another example of somebody with classical EDS, where the shins are easily bruised, and so they have that aged, bruised appearance – that yellowed – but on top of that is a lot of these atrophic scars, from simple, easy wounding and wounds that haven't healed as well as they should. And so, most of us would look at that and say, "What happened?" Okay. Or "Who did what to that child, with a child burn, child in an accident, whatever else?" and that was part of the condition.

[00:10:21] This is aa a picture of somebody else with that very superficial veiny pattern that we look for in vascular EDS, and I will tell you it's hard, because there's many aspects of, of our bodies, where there are times where the veins are more visible, and it does worry a lot of people. Do they have vascular EDS? I think it's a fairly subjective kind of thing and it's difficult to use that, but this is sort of the classic picture.

[00:10:53] So, the typing, the basics of EDS, is trying to figure out where does that patient fall? Where does it fall based on, "Do you have joint hypermobility?" Sometimes it's depending on which joints. There's a small joint versus large joints. The skin features are something that really starts to, start to spread out. You know, a fragile skin and etc. could look like classical EDS. The veiny pattern could be vascular EDS. The soft doughy could be dermatosparaxis, or one of the other types. So, it's one of those things that kind of starts to help us along. Fortunately, of the 13 types, 12 have genetic tests that can sort of help us with our confirmed suspicion. That's the test what they have. The most common, obviously, is the hypermobile tests, and I do appreciate all those who have been part of the HEDGE study, because obviously we need to find a more objective marker to sort of move things forward with hypermobile EDS.

[00:12:03] Outside of that, there are other systemic manifestations. Some can be bone related. Some can be vascular related, but a lot of that can overlap among the different types. So, we do have to be aware of joints, skin, and then sort of like other, and it's still part of the connective tissue knish. But then complications related to that chronic widespread pain, multiple dislocations, premature disc degeneration and fusion, chronic fatigue, POTS, a lot of the things you're going to sort of hear.

So, most of our EDS forms have other systemic disorders and so it's one of those things that we again, have to use to help us type, but once we're sort of in the ballpark, fortunately, the DNA genetic testing does a pretty good job of helping us sort it out. The one caveat is, I will tell everybody when I tell my patients, genetic testing is powerful, but at the same time it's sometimes uninformative. Which means I tell everybody it's like a pregnancy test. You're pregnant. You're not pregnant. You could be pregnant.

[Laughter]

I look pregnant, but I'm not. I took the tests...

[Laughter]

...but it's just one of those things that can really confuse people, because if you're not sure that the patient has a particular disorder, and you get an ambiguous test, a lot of times you don't know what to do with them. And it doesn't mean you shouldn't do the testing, it's just that you should try to put that all together as a picture. The genetic testing itself, should not always drive what you think about the patient. That comes from a geneticist. That comes from somebody who used to run genetic labs. I will tell you that is not the end-all, be-all of things, despite how much hype genetics is getting as far as the testing and stuff. I wish it was as easy as CSI. That I could swab somebody and tell you in 30 minutes. Alright.

[00:14:06] And I want to thank you for your attention and I think I will turn things over...

Oh! I, I have an extra slide in all my slide sets, because I wasn't sure where would it go. I think this is a good spot. So, in previous talks, in previous times, you may have heard that we've been trying to work on the diagnostic codes, because one of the confusions among EDS — when we communicate amongst health professionals, is there's one code for EDS. So, if you're a person with vascular EDS and you show up to the hospital, and it says EDS, but the ER physician has seen 90 POTS patients with EDS, they're not going to pay attention to the one who might have vascular EDS, and that's a dangerous situation. So, we've been working, kind of behind the scenes, to try to develop, try to get those codes broken out. It didn't quite happen the way we wanted to and there have been bumps along the way, but I saw this a week or so ago. I don't know if you guys have seen it.

[00:15:14] We will have new diagnostic codes for EDS.

[Applause]

So, I'm very happy about that, because it does mean one, our work paid off, and two, is this will help to some degree. Obviously, didn't break out in all thirteen, which was our wish list, but it will help in communication, so that when we mean classical EDS, somebody knows that that patient is classical EDS, based on even the code, because sometimes those text descriptions for that doesn't translate as easy as the codes do. So. Alright that's all I have. I swear.

[Applause and "EDS 101" ends]

[00:16:02] *["HSD 101" begins]*

[00:16:07] **Dr. Alan J. Hakim**:

Right. So, I'm going to follow on then from Brad. Hypermobility spectrum disorders, room 101. I'm not sure about "Room 101", because when I watched the program on TV in the UK, the whole idea was were supposed to dump it in room 101, and get rid of it. So, I think I get it. We're not gonna dump this. I hope not.

[00:16:29] So, just reintroducing this concept of Ehlers-Danlos syndromes, first, in order to give some context around hypermobility spectrum disorders. Back to the comment in a slightly different way, but same message from Brad, that we absolutely recognize the syndromes as a combination of musculoskeletal pathology, skin manifestations, and other connective tissue, and you saw from some of Brad's slides, the nature of the other connective tissue pathologies that they can be. Whether they be, for example, ocular, gastrointestinal, possibly vascular – these are all the things that we're talking about when we describe the other connective tissues. And of course, this familial tendency, whether it may be dominant or recessive in its genetic nature, but clearly a tendency to run through families. And then this other really important issue that we recognize a number of related conditions that we don't, at this time, use within our diagnostic criteria, but we completely appreciate add substantially to the complexity of our patients' presentation, and here I'm talking about things like the cardiovascular autonomic dysfunction, for example. So, if we take that model and start to think about the concept of hypermobility spectrum disorders, what's the difference? So we're going to look at that, and then we're going to have a look at the historical context that led to this particular classification.

[00:18:25] So, take the same idea of the Venn diagram with the musculoskeletal, and the skin, and the other connective tissue, and what I've tried to suggest here in this particular diagram is that the big-ticket item for the hypermobility spectrum disorders is the musculoskeletal issues. It may well be that there are one or two unusual skin signs, or maybe one or two of the connective tissue disorders that are, that are very, very mild and present, but they're not sufficient for us to consider within the current criteria structure as enough to guide us towards a diagnosis of Ehlers-Danlos syndrome, and so our focus very much in the hypermobility spectrum disorder diagnosis, is that the manifestations of the musculo-skeletal problems. We do also recognize that this can – it's – we have a

sense that this is familial. That they're the issues that I'm going to describe to you can also run through the generations.

Just as important though, I flagged it at the bottom of my slide here, is that we also recognize that the hypermobility spectrum disorders have a similar pattern of related conditions that can cause complexity to their presentation. In Ghent last year, at the international scientific meeting, we had presentations during the hypermobile EDS session, on the fact that, for example, pain, and fatigue, and cardiovascular, and gastrointestinal autonomic dysfunction can appear with the same kind of prevalence and the same kind of issues, problems, in HSD as well as in hypermobile EDS. And this has been a really important message for us to try and get across, both to our clinician colleagues, and also to our patient groups. That separating out the two diagnoses does not in some way make HSD more benign in terms of the complexity of some of these other problems that can arise.

Now this doesn't surprise me as a clinician, who also with in rheumatology, sees a number of patients who have pure chronic fatigue syndrome or primary fibromyalgia, and indeed, a number of other chronic pain disorders, because we see in the whole patient group, this manifestation of these other complex disorders. So, these conditions that I've just been describing don't necessarily, even in themselves, separate out HSD and EDS from other chronic pain disorders. There's clearly a mechanism going on that we have yet to fully understand. The most important thing is, we don't have to yet understand the why, we have to learn to recognize and treat them now. And that's the message that we're really keen to get across at the moment was, we explore the basic science of this.

[00:21:34] So, when I'm sitting in clinic and I'm trying to work out, from a, an assessment point of view, and this has to include a full physical examination. You cannot do this sat the other side of the desk from somebody and make it up. You've got to examine your patients. So, if any of you have felt that you haven't really had a good run for your money with your clinician because they've been sat the other side of the table and told you what the answer is, I suggest you go either somewhere else, or if they are sensitive and receptive to this, you go back and you get a physical examination, because I have been doing this for more than 20 years and I could not tell you the diagnosis by looking at you. I might have a rough idea, but you've got to examine.

So, the difference here really, fundamentally, between hypermobility spectrum disorder and hypermobile EDS, is essentially, the skin, the presence of the skin pathology, the tissue fragilities, perhaps even the marfanoid body habitus, but the similarity, which I think is the key thing here, is the presence of hypermobility, other structural issues in the musculoskeletal system – which I'll come to in a moment– and the pain, and the fatigue. These are fundamentally identical. One of the key important differences though, in the way we describe this in the hypermobility spectrum disorders, is that we recognize that you don't have to have generalized joint hypermobility for this to apply to you. You may well be an individual who has one unstable complex joint that's causing you a lot of grief. It would be applicable, at that time, to describe you as having hypermobility spectrum disorder, should we wish, or we could just simply say you have a dislocating, highly unstable shoulder. The terminology is interchangeable.

One of the other things about HSD as well though, is that you may be unwell with your hypermobility and the mechanical problems from it, and respond to the relevant treatments, primarily physical treatments, and therefore return to a sense of normality and be hypermobile and well. So, you can move from being well and hypermobile to being injured and within the spectrum, to being treated and managed, and returning to normality. This is why it's a disorder. It's not a disease, it's not a syndrome. When you look at the syndromic side of things, you cannot change the scars on the skin. You cannot change the tendency to the bruising. You cannot change the tissue fragility. These are all there for a reason that we're trying to understand more formally, biologically, but although we can, we can manipulate, and improve, and reduce risk of further injuries, you cannot change a syndrome of that nature. Once you're in, you're in. Sorry.

[Laughter]

But with hypermobility spectrum disorder, you can go back to a sense of normality. With time, you might actually develop new signs, which actually means that you may move towards something that looks much more familiar to us as the hypermobile variants of Ehlers-Danlos syndrome. So, it's an awkward time, when you sit in the diagnosis hypermobility spectrum disorder, if you worry about that. If you focus on the management, primarily of the musculoskeletal condition, and the fatigue, and the functional impact that that's having, then there's an opportunity for a lot of the issues to resolve and not to worry about the diagnosis.

[00:25:50] Okay. So, these are the key issues that we're exploring that are common to hypermobility spectrum disorders and to hypermobile EDS, and of course these would apply in varying degrees of increasing severity, potentially, in all of the other variants of Ehlers-Danlos syndrome. The joint hypermobility, the joint instability with subluxations and dislocations, the injury to ligaments and tendons and soft tissues, reduced awareness of position — proprioception. I've been doing the HEDGE work this morning. It's been absolutely fascinating watching people falling all over the place, and don't know where their arms are, and "No, sit here. No not there. Here." You know? "What's wrong with you?"

[Laughter]

There's a lot of really, really good work. I'm not talking about it here for this particular meeting, but I am talking to the clinicians on Friday. There's a lot of fantastic work coming out that's been published over the last three or four years on proprioception from a much more functional perspective, and it's absolutely real. You know, you're not just clums — well you are clumsy but...

[Laughter]

...but it, you know, it's absolutely real, and so, you know, recognizing this as a risk for injury: why do some hypermobile people injure? Why do some not? Well, maybe the proprioception is part of the element to this. Certainly, the instability, and the subluxations, and the dislocations is an obvious reason for, for injury and so hypermobility spectrum disorder patients, like hypermobile EDS patients, will develop joint pain that we call arthralgia. They may develop muscle pain, myalgia, and therein is a little bit of a rub, because if the person who's assessing you only hears the muscle pain and doesn't look at you more formally, they'll start to think fibromyalgia in its purest sense, as opposed to the wider assessment that they need to make of you, and nerve pain, neuralgia.

The fatigue, the marfanoid habitus — we're not sure about at the moment. We're working on that as to whether it's a particular feature, whether actually, we should be flagging for people to have a more formal assessment for Marfan syndrome in that situation, and the family history and other similar concerns. And the thing about all of these different issues that are all primarily musculoskeletal, is that this leads to these considerable issues in terms of changes in movement pattern, in terms of

changes in physical function. I am warning you now, that as I see you walk down the corridor, I am watching you...

[Laughter]

...I'm gonna – I'm not going to try and mimic some of the gaits that I see, because I would probably dislocate my own hip, but it, you know it causes people to inevitably find different ways of trying to function, and that of itself can potentially cause more problems, and so it's a very, very physical phenomenon.

[00:28:54] Okay. And I just put these two images up for you, because I think a lot of, a lot of people struggle with subluxation versus dislocation. The instability story. When I examine patients in clinic, I am almost always finding instability in the form of subluxation in many of the joints. You can wobble their wrists around, and you can wobble their shoulders around, and they also say, "Let me pop the hips in and out for you," and their ankles will twist, and they trip over in the breeze, you know. These are all examples of instability with subluxations sitting around that they are not dislocating, and yet until they've actually come to meet with somebody that can understand their perception of what's going on and talk to them in their language, many, many patients will tell us that they're dislocating. And they're actually not, thankfully, because when you do dislocate, boy do you know that you've dislocated, right? Some people tell me, "Oh, I dislocate my hip." Really? I think you might be subluxing.

That said, I have seen people dislocate their hip and it is horrendous. So, the really important thing, when you're having this conversation with your with your doctors, with your therapists primarily, is "Am I slipping along the joint line and subluxing, and is this causing more stress and strain to my joints, that's causing the issues?" or "Am I actually dislocating?" What's actually going on, because the approach to these things can be very, very different. And so there on the right-hand side of your screen, is an example of an image showing your subluxation, and there on the left hand, an actual dislocation. It's come right out. Now, of course some people are so loose in their joints, that they dislocate, and then by the time they've got to the emergency room, it's just decided to pop itself back in again, and then nobody believes that anything ever happened. I saw somebody in the HEDGE study today, I don't think I'm infringing HIPAA because I won't mention their name, who told me that they were in the shower and they shook the shampoo bottle, and the shoulder popped out. And they went to the doctor, and the doctor said, "Yes, but what did you do?"

"Well I got in the shower and I shook the shampoo and my shoulder popped out."

"Yes, but what did you do?"

So, guy, listen to this woman! She got into the shower and she shook the shampoo bottle and a shoulder slipped out. Okay? She's got a really unstable shoulder. It doesn't take very much to – certainly doesn't take a medical degree to hear that.

[Laughter]

[00:31:37] Just to remind you then, when we are comparing hypermobility spectrum disorder to the other conditions, that we also need to continue to recognize the related conditions, and how these add to the complexity. Marco Castori is probably going to come up a few times, because he and his team in Italy have been doing some amazing work with their patient cohorts, but in April this year, he and his team published a beautiful paper, where they looked amongst their patient cohorts for comparison between pain, fatigue, and autonomic dysfunctional issues in HSD and hypermobility spectrum disorder – and, sorry – and hypermobile EDS. Who put all these Hs and Es and Ds and S in this? Nightmare. And what they were able to demonstrate, is that in both groups, the prevalence and complexity of these related disorders was absolutely the same, and the impact that it had on quality of life was absolutely the same, and I think this is a really, really important message. In addition, they started to explore the way in which clinicians could actually ask the right kind of hierarchical questions.

So, they got to the nub of the issue, because there's an awful lot of complexity there, and it was a really, a really inspiring paper, which I had the privilege to write an editorial for, and I believe through our social media, we've actually shared that and a little bit of background to that with our members and family within the EDS community.

[00:33:22] Okay. So, how did we, how did we get here? Now this, I have to say, is very much a kind of personal view, but I think it probably reflects 95 to 98 percent of the truth, and so forgive me, people like Professor Rodney Grahame, who's in the room with us today, if I have slightly not got it right, but I'm going to try my best.

So, if you look, first of all, over on the left-hand slide – side of the slide, you'll see that I've put the term up there "1969" and the five

type classification for Beighton. This was probably one of the first real classifications that took account of some knowledge of the histology of skin, and the presence of possible genetic variants. Within it, was a particular diagnosis, or classification, called EDS Benign Hypermobile type. This was going to become what we now know as hypermobile EDS, but prior to that, I've put just below that, yeah, another note, that in 1948, and I only know this because I was asked to write a historical paper, and so I went trawling the literature. In 1948, at the Mayo Clinic, Johnson and Johnson were giving a presentation on extended families. And they had families with four generations, and they'd been looking at skin pathology – they were dermatologists – and there's this beautiful – I don't know is any of you read the Mayo literature, I don't blame you if you don't, but they do a little narrative of the presentation and the discussion, and somebody makes the point that they believe that there is a minor variant of the familial disorder that Johnson and Johnson were talking about, which actually turned out to be classical EDS, in the general population, and they said, "We think it probably makes up about 1% of the general population." Well, if anybody ever tells you that this is a new disorder and that we're making it up as we go along, take them back to Johnson & Johnson's paper in 1948. Dare I say to even take them back to before then, to when Ehlers and Danlos were describing that, and dare I say take them back even before then, if you like, to Hippocrates, but that's going a bit far, and just say, "You don't know your history."

Now, let's move forward from there then, to 1997, to the Villefranche criteria, and this is where we actually start to gather a little bit more information from a genetic point-of-view, and we start to use the number nome – nomenc – nomenclature, that would...Numbers. We start to use numbers. Numbers then get changed into names, because it seems a much more appropriate way to describe the phenotypic characteristics.,So, by the 2000s, we're moving down the line, and we have hypermobile type of EDS, EDS-HT or EDS-HM.

So, I'm just going to hold you there then, on that side, and take it to the other side of the slide. At almost exactly the same time, three incredibly brilliant rheumatologists in the United Kingdom, Kirk, Hansel, and Bywaters, were describing this mechanical phenomenon in joints that I've just been alluding to, and realized that it was related to hypermobility, and called the hypermobility and the instability in the injury, hypermobility syndrome. Great. So, on the one hand, we had dermatologists and

geneticists who were starting to explore this, and on the other hand, we had rheumatologists.

Forward, fast-forward to 1997-98, almost exactly the same time that the Villefranche criteria is being developed, comes the concept of benign joint hypermobility syndrome, for which my esteemed colleagues, such as Professor Rodney Grahame, were authors. To become eventually, joint hypermobility syndrome, dropping the "benign," because the realization that there was nothing benign about this. At some point, though, everybody started to have a conversation and say, "Hmm. This patient in clinic with joint hypermobility syndrome looks like this patient in clinic with hypermobile EDS. Hmmm... What do we do about this?" And so, from the 2000s, this discussion starts to, starts to kind of, sort of, flower.

[00:38:05] And this was the sort of problem, and it was being questioned in several pieces of literature, including lead authorship from Brad Tinkle. So, you're hypermobile and you have an injury, but you don't have a syndrome. Okay? Hypermobility syndrome, that's your diagnosis. Okay? Or, well actually, no, you have Ehlers-Danlos hypermobile type. That's your diagnosis. And then finally, just to add to the fun, no, well actually, you don't you have JHS forward slash EDS-HT. Now, if I was confused in clinic, you're going to be confused in clinic, and everybody's confused, and so we needed to do something about this, and that's really part of the reason why the 2017 criteria were developed.

[00:38:55] So, let's take you back, then, to that point in the late 2000s, where we are talking about a label, if you like, in clinic, of JHS forward-slash EDS-HT in patients that we recognize really could sit in either set of criteria. This works for some patients with joint hypermobility syndrome, but if you look at the criteria for joint hypermobility syndrome, the two major entrances in, were the presence of hypermobility and the presence of chronic pain. Now, if you go back to where I start with my slides, and you go back to what Brad was saying around what constitutes EDS, of itself, a presentation with joint hypermobility and chronic pain as a diagnosis of JHS, would be insufficient to make a diagnosis of EDS, because you haven't got the skin issues, you haven't got the tissue fragility issues — it's not that we've missed them, they're not there. You were given the diagnosis of JHS because you presented with a mechanical problem, with pain, but there's no other features going on to suggest that you have a syndrome.

So, if you do pull the two together, and you call it JHS forward slash EDS-HT — we were getting really good at this — what do you do with those

people that actually aren't really JHS forward slash EDS-HT? What do you do with them if you develop a new set of criteria, which you know, I think are clearly represent what we believe hypermobile EDS more or less is? What do you do with those other people with mechanical problems? And the answer is, you need to find a home, because you can't just leave this kind of patient group high and dry. They have their own set of complex issues and so, as I've tried to show you on here. If over on the left of your slide you have a line in the sand, if you like, you're either in because you fulfill the criteria...what happens if you are on the right hand side of that line, with the mechanical issues, but you don't have features of EDS or another heritable disorder of connective tissue?

[00:41:10] Also, what happens if you don't have generalized hypermobility? Because all of the EDS conditions make an assumption that primarily, your hypermobility is widespread in your body. What happens if you only have a few regions, or sites, or a single joint in your body that's hypermobile, unstable, and injuring? What do you do? What, what do you do in this situation to try and help somebody? Place them in the right context, so that you can give them the right treatment.

[00:41:41] And that's what this slide is, is just highlighting that in terms of difference in understanding the nomenclature.

[00:41:48] I'm going to get that right one day: nomenclature. Right.

Thank you again to Marco Castori, and this is his slide of the historical context. On the right-hand side, we had joint hypermobility, symptomatic joint hypermobility, and within that, two groups: the JHS group and the hypermobile EDS group. Now, in the present, we recognize joint hypermobility in the general population, the hypermobility spectrum disorder, and then hypermobile EDS. So, this is one visual way of conceptualizing it. This is my visual way of conceptualizing it. Continue with the, with the zebra motive. We start over on the far right-hand side, with this kind of gray, unclear group that have got mechanical problems, but are not syndromic. We then move over the line because we've met the criteria for a diagnosis of hypermobile EDS, and we then move over the line again, because it's clearly more complicated in terms of the likely pathologies and presentations, towards the rarer types of the Ehlers-Danlos syndromes, and so this is how we now conceive of that spectrum of the range of disorders within the patient population that we look after.

[00:43:10] To finish, coming back to the point that hypermobility spectrum disorder can be just as complicated, because of the multi-faceted nature. It's really important in our trade treatment programs, to be cognizant of the physical issues, the physiological issues, like autonomics, the functional impact that this has, the social impact that this has, the behavioral changes that it might lead to, and the psychological health stressors that can arise. It is not good enough for anybody to say you have hypermobility spectrum disorder, go off and swim and walk, go away. It is usually much, much more complicated than that, and needs to be given the respect that it deserves.

[00:43:49] Thank you, very much.

["HSD 101" ends]

[00:43:56] *["Genetic Testing 101" begins]*

[00:44:00] **Dr. Clair A. Francomano**:

Wow! It's so great to be here. It's so great to see so many old friends and just such a wonderful, wonderful event.

So, I hadn't planned to talk about Indiana, but I will be moving to Indianapolis in September and I'll be joining the faculty of Indiana University School of Medicine. I'm delighted to have this opportunity to pursue research and to be involved in the education of residents, because we need so many new doctors who are interested and knowledgeable about Ehlers-Danlos syndromes and the hypermobility spectrum disorders, and of course, I'll be continuing to take care of patients. So, I look forward to that. I think it's a very exciting opportunity, both for myself and for the Ehlers-Danlos and hypermobility spectrumdisorder community.

So, today my job is to give you a brief introduction to genetic testing.

[00:45:03] And this cartoon illustrates the hyp—, the human genome, and the gentleman is saying once you unfold one of these things that's never the same. So, by unearthing the sequence of the human genome, we certainly unearthed a whole bunch of different dilemmas: medical dilemmas, insurance issues, privacy issues, and moral issues; but in order to get to those things...

[00:45:32] We first have to figure out how to apply the genetic testing. It all comes back to the DNA, which is our genetic blueprint, and DNA stands for deoxyribonucleic acid. We find it in thenucleus of every single cell in our

body. It's wrapped up in structures that we call chromosomes, and in each of our cells we have 46 chromosomes. There are 23 pairs of chromosomes in each cell.

[00:46:06] Now, these are the building blocks of the DNA. The building blocks are called nucleotides. Each step on that ladder there is an example of a nucleotide, and each nucleotide has a sugar, a phosphate, and a nitrogen base, and those nitrogen bases are the As, Ts, Gs, and Cs that make up the sequence of the DNA, and it's the order of those bases that provides the sequence of the DNA.

[00:46:44] So, when we think about genetic alterations, there are a number of different types of genetic alterations that people can have. You can have abnormalities in the number of chromosomes. So, for example, if you have three of a particular chromosome, rather than two copies of the chromosome, that's called a trisomy, and Down syndrome, or trisomy 21, is an example of that. Or, you might have a monosomy, where you're missing one of a pair of chromosomes. So, that's one type of genetic alteration.

[00:47:20] There are also chromosomal changes that we can see. So, we may have a deletion of a piece of a chromosome, and the way we determine that is by looking at the chromosomes under the microscope, and what we call a karyotype. There can also be a translocation, where a piece of one chromosome is moved from one chromosome on to another chromosome. Or an inversion, where you have a piece of the chromosome that's just flipped upside-down. In general, though, when we think about genetic testing, we're thinking about a class of alterations of the DNA that we call single gene changes, and these are where a small nucleotide change in a segment of the DNA that codes for a gene, is observed.

[00:48:15] Now, before I get to the specifics of that genetic testing, we have to think about inheritance, because this plays a role in the way we think about genetic testing.

[00:48:26] So, going back to those cells: the 46 chromosomes in 23 pairs, we inherit one copy of each of our chromosomes from our mother, and one copy from our father. So, when we think about the genes that exist in pairs, one copy from each, of each pair comes from our mom, and the other one comes from dad.

[00:48:53] In the process of what we call gametogenesis, or the formation of eggs and sperm. We have what's called reduction division, where the number of chromosomes is reduced down to 23. Whoops! Are we there? Okay.

One, one from each parent, and then at fertilization, when the egg and the sperm come together, we go back up to 46 chromosomes.

[00:49:28] So, in dominant inheritance, we have a situation where one version of the gene is dominant over the other. A single copy of a variant in that gene, is sufficient to cause a condition. So, an autosomal dominant disorder might be inherited from one of the parents, or it may be a result of a new change in the DNA that happens in the process of the formation of the egg or the sperm. With autosomal recessive inheritance, you need two copies of the altered gene. The condition is expressed only when you have two copies of a genetic variant at a single gene, and you've gotten one from each parent. The parents are said to be carriers in that situation. They have a single copy, which generally does not manifest in terms of any physical manifestations. And X-linked inheritance, caused by genetic variance carried by the X chromosome.

[00:50:43] So, just some examples of conditions caused by some of these different DNA changes: An abnormal number of chromosomes, as I mentioned — Down syndrome, is an example where we have three copies of chromosome 21. There are a couple of other syndromes called, one called Cri du chat, one called Williams syndrome, that are results of deletions in particular areas of the genome. And then single gene mutations, cystic fibrosis and sickle cell anemia are examples of these. But what we're most interested in today of course are the Ehlers-Danlos syndromes.

[00:51:24] And this illustration is from Joanna Amberger and colleagues at Johns Hopkins, who put together this lovely daisy that illustrates the thirteen different types of Ehlers-Danlos syndromes that were described in the 2017 classification, and the genes that are known to cause each of those conditions. And of course, you see in the lower right-hand side, the hypermobile type is that orange petal with "unknown" written in there. That's the only one of these thirteen types, which in 2017, did not have a known gene or genes underlying the condition, and all the rest of them, the molecular cause is well understood. And so, there are gene tests available for each of the types, other than the hypermobile type.

[00:52:34] And this was a list of the classification. You saw this from Brad Tinkle as well, with the type of inheritance for each one of them. You can see the classical type, and the vascular type, and the hypermobile type, as well as the arthrochalasia type, are all autosomal dominant, and the, most of the rarer types are autosomal recessive in inheritance.

[00:53:06] So, what are the types of tests that we can do? What kinds of questions might we approach a geneticist or a genetic counselor to ask about? We can do diagnostic tests, and diagnostic tests are used to really either confirm or establish a diagnosis that's suspected, based on particular physical signs. There are predictive tests that help us to look for gene mutations or variants that are associated with disorders, that may appear later in life. So, for example, a risk of breast cancer, or a risk of colon cancer. Carrier identification is used by people with a family history of recessive disorders, if they're interested in knowing what their risk might be of having another child with a recessive condition. And we do prenatal testing, to test a fetus, where there's a risk of the fetus having a particular genetic disease. Newborn screening is used once a baby is born. And there's a whole field of forensic testing, Dr. Hakim mentioned CSI, to identify an individual for legal purposes. And then finally, research testing is used to find unknown genes or identify the function of a gene, and that is what our HEDGE study is all about. To try to find the gene, or genes, that underlie the hypermobile type of Ehlers-Danlos syndrome.

[00:54:50] So, what happens when we go in for genetic testing? We take a sample of cells. We might do a blood test or sometimes you might spit into a little tube. Takes a lot of saliva. It takes a long time. And then the DNA is extracted from the cells in the laboratory. The DNA is cut up with specific enzymes and the DNA fragments are separated. They're sequenced and then we use molecular technology to analyze those DNA fragments and give us the actual sequence of the DNA. And really, there should be another item on the bottom there that says that sequence is compared to the reference sequence from the Human Genome Project. So, we want to know, are there differences in this sample that we're analyzing, compared to what is considered to be the reference sequence.

[00:56:01] And you can see why we have to automate this, because if you had to look at every single one of those little dots on there, you would go blind in about 10 minutes. And the automated DNA sequencing machines are used to give us the output of the DNA sequence.

[00:56:23] So, there are several different types of tests that we can perform. We may do single gene testing if we have a very high suspicion that it there's a particular gene that might be involved in the person's condition. There are multi-gene panels now, for example, there are a number of laboratories that will test all of the known genes involved in all of the various types of the Ehlers-Danlos syndromes. So, you can send off an EDS multiple gene

panel, or there are other panels that caught – do all the genes in – known to cause aneurysms. So if there's a family history of aneurysm, and a suspicion that it might be vascular Ehlers-Danlos syndrome, but it might also be one of the other hereditary disorders of connective tissue that causes an aneurysm. You can cast a wider net and do one of these panels. Whole exome sequencing looks at the sequence of every single one of the known genes. There are about twenty-four, twenty-five thousand of those now and whole genome sequencing looks at everything. So, all the regulatory regions in the DNA, all that stuff that we used to call junk DNA, that we now know probably plays a very important regulatory role. All three billion base pairs in the DNA is sequenced when we do whole genome sequencing.

[00:57:55] So – and by the way, we're able to do that whole genome sequencing now, because the cost of DNA sequencing has come down so drastically over the last fifteen to twenty years. As I mentioned in the out, the breakout session this morning, I was – recently heard somebody speaking about this, and he said that if the cost of cars had come down as much as the cost of DNA sequencing has over the last twenty years, we would be able to go out and buy a Toyota Corolla for a quarter.

[Laughter]

So, that has enabled us to do sequencing in a way that is generally available. We can, we can offer whole exome and whole genome sequencing in a way that was strictly unimaginable ten to fifteen years ago.

So, what are the possible outcomes from this genetic testing? We may find there's no variance in the gene or genes of interest. In other words, we're unable to make a molecular diagnosis, or we have excluded the diagnosis which was our original suspicion. We might find a change in one or more genes that we're interested in, and that change is going to be classified by the molecular diagnostic laboratory in one of five ways.

They may say that it's pathogenic. In other words, it's disease-causing and it explains the person's condition.

Or that it's likely pathogenic. It's most probably causing a disease, but not a hundred percent certain.

There may be something we call a variant of unknown significance, which means there's a change there, but we really don't know what it means.

Or it may be considered likely benign or benign.

And there are algorithms that the laboratories use, based on the level of evidence that's available, in terms of the evolutionary features of this particular variant, and whether it's been seen it other people in the general population before, and whether the variant is likely to change the amino acid it involves in the terms of its structure and function of the protein.

So, if we get a pathogenic, or likely pathogenic result, that likely will explain the question that we're asking, but the variants of unknown significance, I sort of feel like those just, it's as if we hadn't even done the test. We don't have any more information now than we did before we do it, and so we don't make any clinical recommendations. We don't make any changes in our management plan based on variants of unknown significance. It's important to recognize that we may also find a variant in an unexpected gene as a result of this testing. And we may also find unexpected family relationships. So, we may find that the person who thought they were the father of this child, is not really the father of this child. So, it's important for people to recognize these potential outcomes before they go into the whole process of genetic testing.

[01:01:35] So, that is a very quick run-through of an extremely complex subject, but it's an introduction: your genetic testing 101, and I'll be happy to answer questions during the panel. Thanks, so much, for your attention.

["Genetic Testing 101" ends]

[01:01:54] *["Q&A Panel" begins]*

[01:01:55] **Lara Bloom**:

So, if I could so if I could ask Brad, Clair and Alan to come back up on stage, please, for the Q&A. A couple of questions that came in about ECHO, just quickly: Someone asked that they're a medical professional, they reached out to try to sign up to our cohort, and they couldn't get on because there were no more spaces. Well, we're launching the second cohort that's starting in September. Just make sure that anyone you tell signs up to our newsletter, and as soon as we have new opportunities to sign up, they will be sent all the information.

Someone else asked if they could send, share the link on platforms. Frankly, you can share that link wherever you want. As many places as you possibly can, so please, please do.

Okay. Questions for you all. Mitral valve prolapse: is it still a risk for hypermobile EDS, and should you get tested?

[01:03:02] **Dr. Clair A. Francomano**:

Mitral valve prolapse is still included in the diagnostic criteria for the hypermobile type of Ehlers-Danlos syndrome, and so I, my personal practice is to recommend echocardiograms for any person in whom I suspect that diagnosis.

[01:03:22] **Lara Bloom**:

Thank you. So, are you saying that perhaps along the spectrum of HSD to hEDS, that there could be a point of no return event? Meaning up into a certain point, it's reversible, but yon – but beyond that point now called hEDS, it becomes irreversible, and if so, any speculations as to what that event could consist of?

[01:03:45] **Dr. Alan J. Hakim**:

So, it's not really an event. This is, this is something conceptual around criteria and classification. When I say that you move from one to the other it's, it's on the basis of a description of what is happening to you, as opposed to something has to happen. You know, there isn't an event zero, or whatever it – a horizon event, or whatever it is – that suddenly leads from one diagnosis to another.

The point I wanted to make about hypermobility spectrum disorder, primarily, is that you may have an injury to a hypermobile joint, and/or a group of hypermobile joints, and recover from that to essentially be back to being hypermobile, and otherwise no different from other hypermobile people in the general population. If you have a diagnosis of hypermobility, of hypermobile EDS, you have that diagnosis because you have fulfilled the criteria for that diagnosis, and many of the features in that, it's not that they're not reversible, it's that they are there, and they are there for reasons that we're trying to learn to understand. So, the papyraceous scars, the piezogenic papules, the stretchy skin, these are not reversible. You have the features of a syndrome. I cannot imagine, intellectually, how you would revert from that back to a state of normal, in terms of not fulfilling the criteria. Does that mean that you have an abnormal life? Of course it does not. What it means is that you've got various characteristics that make up the diagnosis, and from there, we try and normalize somebody's well-being.

[01:05:38] **Lara Bloom**:

Thank you. At what age can you reliably check for hEDS?

[01:05:48] **Dr. Brad Tinkle**:

It's kind of a loaded question, for different reasons, because hypermobility is something of a spectrum, as far as the age of presentation, etc. One is, we don't recommend that younger kids be diagnosed. Doesn't mean we don't recognize there's hypermobility and whatever else, but we're kind of careful. Part of it is, many of us have seen young boys, are kind of to the question of that zero event. Plenty of kids who are hypermobile, who then don't go on to have any additional problems, and yet now, you know, starting at three or four, we've labeled them with hypermobile EDS, or some other form. So, I get it. I personally get a general sense, between four and six. Most of time, when I see the families, it's not so much about, you know, the diagnosis of — these are the things you're gonna hear from me at eleven and twelve: good posture, good mechanics, activity, hydration, etc. These are things I want you to start to do. In some ways, they're EDS specific, but a lot of ways, they're healthy lifestyles. So, a lot of times, what we're doing, is trying to sort of coach their family to minimize anything in the future. I would love for a lot of them never develop any symptoms and go forward. So, I'm leery to give a diagnosis early. I don't mind seeing them about four or six, to kind of get a general sense if they're very hypermobile or not, but I still honestly kind of shy away from pre-pubertal kids, giving the diagnosis.

[01:07:28] **Lara Bloom**:

Thank you. Does genetic testing from before 2017 need to be looked at again? For now, no mutations, or were the genes attached to the new criteria already known in a genetic testing panel from before 2017?

[01:07:47] **Dr. Clair A. Francomano**:

So, I guess it would depend on the specific test, because a lot of those genes were being unearthed in the early 2000s and the early teens, in the year, in 2010 to 2017. I didn't mention, but I would like to mention that if a person has genetic testing and a variant is found, it's a really good idea to kind of keep coming back to those variants and seeing if they've been reclassified, because they often are, and so re-touching base with the geneticist again every couple of years is a good idea to see if the variants have been reclassified.

[01:08:31] **Lara Bloom**:

And another one for you, Clair. Can you speak to what you think any

hormone aspect could be involved in EDS? Just maybe even alluding to the fact that this is something that came up as a research priority, and that we need to know more. It's a question that's come up in a few different forms.

[01:08:54] **Dr. Clair A. Francomano**:

Right. Well, as Lara mentioned, this is really something that we're very, very interested in looking at, just because we, we see in the clinic that so many more women present with complications and impact on their quality of life than men do, and we consider this to be what we call an autosomal dominant condition, which means that theoretically we should be seeing the same number of people in the men and women categories. And Brad mentioned in his presentation, that there are differences that we see in generalized joint hypermobility from men to women, and as they get older, and we believe that this is related to hormonal changes. So, it's an area that we really do need a lot more research and into the field.

[01:09:40] **Lara Bloom**:

Thank you. Are stem cell treatments or therapies the future of treating EDS?

[01:09:53] **Dr. Brad Tinkle**:

I will tell you that FDA just came out with a warning about the stem cell stuff. It's not regulated. So, like most medical interventions, we would love to see the trials. I've heard a lot of great cases, people coming back from Mexico and Europe, and getting stem cell, and saying their diabetes was cured, whatever else. I think it holds a lot of promise, but until better rigorous designs, I would be careful, because I've also heard a lot of horror stories at the same time. So, it's one of those things that has a potential, because your collagen does get made over and over. It's not just something you slap up on the wall and it stays there permanently. So, having some kind of genetic change, either because of stem cells or whatever else, has the potential to impact that, but again how much, and whether it works...we'd love to see more.

[01:10:54] **Lara Bloom**:

What is – whoever wants to answer's opinion – do you feel is under-researched and/or under-diagnosed complications of EDS that you wish more people knew about or there was more research in?

Do you want to take that?

[01:11:14] **Dr. Alan J. Hakim**:

In my infinite way, I'm not going to answer the question, I'm going to give you some information, and that is that we have a number of working groups within the collaboration –

[01:11:23] **Lara Bloom**:

Consortium.

[01:11:24] **Dr. Alan J. Hakim**:

Consortium. I get it all muddled up. I don't know how you guys cope. I can't...and we have engaged them in asking those very, or that very question, within their specialty areas. So, there are 14 groups now, and we've asked them for the top three – of course my group gave them the top twenty – and we're collecting that at the moment and I believe that Fransiska Malfait, who is our Chief Research Officer –

[01:11:53] **Lara Bloom**:

Scientific Officer.

[01:11:54] **Dr. Alan J. Hakim**:

Scientific Officer – is collating that at the moment, and we will shortly be publishing that, and that will give you a sense of, amongst all of the medical professionals, rather than just our opinion here, what we think the key things are. I will tell you now, there are a number.

[01:12:11] **Lara Bloom**:

And for those that aren't aware, our International EDS Consortium is divided into committees for all the different types of EDS, and into working groups for all the associated symptoms and conditions. So, we've got a really good range.

[01:12:26] **Dr. Clair A. Francomano**:

If I could just mention, we also had the opportunity last year to work with a group that we called the EDS Comorbidity Coalition. And this was a coalition of different patient support groups, that included The Ehlers-Danlos Society, the Chiari and Syringomyelia Foundation, Dysautonomia International, the Mast Cell Society, the Spinal CSF Leak Foundation, and I'm sure I'm forgetting one or two others, but we went through a process of defining them, what all of those groups thought to be the most important research issues, and the lidocaine study that is being conducted

here, rose to the top, over one at the top. The hormone issue that was questioned earlier, that also came up as well, the role of hormones, and then treatment of dysautonomia through vagal nerve stimulation. So, there are groups now, that emerged from that Comorbidity Coalition, that are working on, and they're at different levels. The lidocaine study, Dr. Raj is obviously very far along with that, because he's conducting it right here at this convention.

[01:13:50] **Dr. Brad Tinkle**:

So my, one of my current sort of pet peeves, is I think we're doing a lot better job of talking about joint hypermobility and stability, and those kinds of things. We – not necessarily outside the EDS community, also talking about that, and I think POTS, and orthostatic intolerance, and stuff, is sort of being talked about. What is sort of sticking with me now, is how many other dysautonomic features are present? From sleep disturbance to GI issues, and etc., that are being unrecognized and being treated a lot of times in contradiction to the other things that we're doing, and it's one of my more frustrating things right now, to sort of deal with.

[01:14:35] **Dr. Alan J. Hakim**:

And then, just maybe one last comment to that question is that certainly, within the list of areas to explore, we are going to be able to categorize these, not just into the sort of more traditional basic science or epidemiology type studies, but how much of what and why, but also really looking to explore the sociological impact, and fundamentally where is the evidence? How do we cite the evidence for impact of clinical treatment? So, clinical outcomes a really important part of our agenda.

[01:15:17] **Lara Bloom**:

Wonderful. And a good – good reminder of why we've kind of asked everyone here and everyone streaming in to help us support what we're doing, because it goes to funding research studies like this, and getting the answers to all these unknown questions.

There's been mention of other connective tissue disorders multiple times, what are they?

[01:15:47] **Dr. Clair A. Francomano**:

So, the Ehlers-Danlos syndromes lie under a very, very, very big umbrella that we call the hereditary disorders of connective tissue. And this is a term that was coined by Dr. Victor McKusick in the early 1970s, and he

wrote the book, the very first book called Hereditary — *Heritable Disorders of Connective Tissue*, I believe was the title. And so if you look at joint hypermobility, and you do a search in OMIM, which is Online Mendelian Inheritance in Man, and it's a catalogue of human genes and genetic disorders, and you do a search for joint hypermobility, for example, you will find over 350 different diagnoses that have joint hypermobility as a feature of their, of those conditions and many of them fall within this umbrella that we call the heritable disorders of connective tissue. Marfan syndrome is one of them. There's something called Stickler syndrome, which involves early arthritis, and hearing loss, visual problems, cleft palate. Those are two of the most common that come to mind, but it's a very, very broad range of conditions, and each of them have their own diagnostic criteria, and their own patient support groups, and their own world. So, it's really a very interesting group of disorders. They're sort of, they're our brothers and sisters that they are in Genetics Land.

[01:17:19] **Lara Bloom**:

Thank you. Is it possible to have two types of EDS?

Step right up, Brad.

[01:17:31] **Dr. Brad Tinkle**:

Well, one thing we say in genetics is, "Never zero, never 100%." So, yes. And I always tell everybody, and this is good advice for y'all, is please do not find your mate at these conferences, because that can happen. When you go to little people conferences, you see that a lot and you just sort of wonder what they were thinking.

[Laughter]

So, yes, but you know, really, most people because there's such an overlap, usually people really fall into one category. They may have features that's more prominent in another type of whatever else. It does behoove us to make sure that we have the typing correct, that's where the genetic testing can be very helpful when we're looking at anything, especially outside hypermobile type, to verify is it what are the other types or not.

[1:18:23] **Lara Bloom**:

Thank you. Clair, you may be a good person to answer this as the PI of the HEDGE study. Why do you think it's been such a struggle to find the gene for hypermobile EDS?

[01:18:36] **Dr. Clair A. Francomano**:

This is an excellent question. I think there are a number of possible answers to that question. One easy answer is that it's unlikely to be a single gene. I think that if there were a single gene that caused hypermobile Ehlers-Danlos syndrome, we would, we would know what it was by now. There have been many investigators all over the world, who have really engaged in top-notch science to try to find this gene, and it has not shown itself to us yet.

So, that's one thing for certain. It's not going to be a simple, one gene, one phenotype relationship. So, likely, there are multiple genes that underlie the condition. I think one other feature or factor, is that before the 2017 criteria were published, we had a very heterogeneous group of people that were being called hypermobile Ehlers-Danlos syndrome. So, it was hard to get a signal, perhaps, from the studies that have, that were being done. So, I'm hopeful that with the 2017 criteria, that that will enable us to narrow it down a little bit.

It's possible that there are many, many genes. There, there is a condition called hypertrophic cardiomyopathy, for which I think now we have about 35 or 36 genes that cause one phenotype, that looks pretty much the same from one family to the next. So, if that's the case, that could be another reason that we've had so much difficulty finding the genes that underlie hypermobile EDS, and it may be that it requires an interaction between genes and environment, or between several different genes, in which case, you know, it's really going to take intensive examination of the DNA sequence, and a look also, at environmental exposures to tell us how this hypermobile EDS phenotype is emerging. So, we have our work cut out for us.

[01:20:48] **Lara Bloom**:

Thank you. What is the inheritance pattern for EDS?

[01:21:02] **Dr. Clair A. Francomano**:

So, the different types of Ehlers-Danlos syndromes have different types of inheritance. There are — some of the types have autosomal dominant inheritance and some of the, most of the rarer types have autosomal recessive inheritance.

[01:21:18] **Lara Bloom**:

Marfanoid habitus has been mentioned. Is it common in non-Marfan patients, specifically in hypermobile EDS?

[01:21:30] **Dr. Brad Tinkle**:

That is still one of our questions, how common it is. Dr. Francomano mentioned Dr. McKusick, so one of the things in OMIM has been recognized, sort of a Marfan body with joint laxity. That was considered sort of a separate entity, and having run a Marfan clinic, I will tell you nine out of ten people who showed up didn't have Marfan, they had a body type, and probably three or four of those had a lot of flexibility. And so, it's something we see, is that the majority of patients know is that 5%, 15%, and etc. Is it a useful phenotype physical characteristic? That's a lot of things we're continuing to sort of study. I think that group does present with a lot of similar features and I'll find like the brother who has that marfanoid body habitus, and the sister with what looks like anything else, hypermobile EDS, and yeah, they have very similar overlapping features. Some of it also depends on ethnicity. I see it more commonly in Eastern Europeans and some other sort of groups, so I think it's one of those things that's probably in there, but could it represent a separate group that eventually we tease out? That's another question.

[01:22:59] **Dr. Alan J. Hakim**:

The other thing that comes to my mind that is different, if you like, from the perception of this and the diagnosis of Marfan syndrome, is that the Marfanoid body habitus is one of a number of possible signs and features that would make up our suspicion of the hypermobile variant of Ehlers-Danlos syndrome, but within the criteria for Marfan syndrome, it's usually quite a dominant feature. That said, if you look at the 2010 criteria for Marfan's, and I'm not sure if they're looking to change it again at the moment, it's actually — it's not that it's been downgraded, but it sort of shifted almost in its priority, in favor of aortic root pathology, and eye lens pathology, familial history, and genetics, is the kind of, sort of more dominant diagnostic criteria. And I think that, of itself, within the Marfan's criteria, reflects somewhat the fact that the Marfanoid body habitus is a relatively general feature that we see in the general population, as much as we do in hypermobile EDS and Marfan's.

[01:24:08] **Lara Bloom**:

If you just stay there, please, Alan.

[01:24:11] **Dr. Alan J. Hakim**:

I only got 10 minutes to answer this question.

[01:24:13] **Lara Bloom**:

As the lead of the hypermobile EDS and HSD group in the Consortium –

[01:24:18] **Dr. Alan J. Hakim**:

Who told you that?

[Laughter]

[01:24:21] **Lara Bloom**:

We have had varying versions of questions regarding the 2017 criteria. How it doesn't suit all. A lot of people are still not fulfilling it, and mainly based on the Beighton score and issues with hypermobility not being as important in terms of their features, could you maybe discuss a little bit about –

[01:24:44] **Dr. Alan J. Hakim**:

Elaborate.

[01:24:45] **Lara Bloom**:

Yes.

[01:24:46] **Dr. Alan J. Hakim**:

It's like that horrible question on the back page of the exam: "Discuss."

[Laughter]

Okay. Well it's a good job I've got nine minutes left. So, what I would say, is that the working group for hypermobile EDS is absolutely exploring this now. We had our first, kind of, face-to-face meeting back in, in, in March for a couple of days, but we've been doing a considerable amount of background work before then, over the previous months, and that, because it led to lots and lots of questions, has led us to be to explore ways in which we can begin to answer some of those questions for ourselves, around what should be changed and why. Or maybe I should say, what should be developed and why, because I don't, I don't see this as a, as a sudden step change, it's very much a development. Now, that does not mean when

we've come to where we think we ought to be, that we then publish this and send it out to the world, and say here you go, have another go. We will then need to spend quite a considerable amount of time working with our clinical colleagues, in particular, and other members of our working group within the Consortium, exploring within our current practice, whether we are better identifying patients that should fulfil the criteria.

Now, what are the key headlines that we're looking at? One of the big problems with the presence or absence of generalized joint hypermobility is that if you score correctly within the Beighton score, then it is automatically assumed that you are hypermobile, and that is absolutely right, because that's how this tool works. If you don't score the relevant four, five, or six on the Beighton score, you are assumed, if you are naïve to this as a clinician, that you are not hypermobile. And the problem with that, is that the Beighton score does not include other areas of hypermobility that we know in clinical practice are fundamental issues for many of our patients. Whether it be TMJ, neck, shoulder, hip – it's sort of – the hip is sort of in there, but people think when you're bending forward it's coming from the spine – and ankle and foot. Now, there are two other major classification criteria that have been published and validated, upper limb and lower limb, and our team are exploring those at the moment to try and work out whether there are elements of that, that we, that we add into this process to make the assessment of the hypermobility per se, a much more logical from the clinical perspective.

Second thing is, what is the importance of the proprioception and the joint instability? It's there in the current criteria, but actually, if our arguments are that many of the mechanisms for injury are not just about the hypermobility, but also about the instability. How do we flag that at – with a sense of priority to it? I don't have the answers for you yet. These are all things that we're asking ourselves, but hopefully these are resonating with you in terms of the logic.

Third element is when you look at the list of the twelve elements that make up the skin and the other tissues. Is within that, can we better cluster and describe the various phenomena? So, should we really have five different things, or six different things that you might have in your skin, or should we have a question that says, "Are there skin problems?" And what does that question look like? Are there other structural problems and what does that question look like? So, those are just a few elements of the sorts of things that we're exploring. We have a lot of work

to do, and we've got some fantastic clinical researchers that are helping us to answer some of these questions, so that we can come back with the evidence for the development that we think there needs to be. I'm not going to predict the timing of this. We are going to have to run it through a lot of clinical practice to make sure that it makes sense before we produce a development of the set of the current criteria. My gut feeling is it will be more inclusive and less increasing – rather than less increasing.

[01:29:05] **Lara Bloom**:

Wonderful. Please, could everyone give a big hand and thank you to all of our speakers today.

[Applause]