The Ehlers-Danlos Society
P.O. Box 87463 · Montgomery Village, MD 20886 USA
Phone: +1 410-670-7577

The Ehlers-Danlos Society - Europe
Office 7 · 35-37 Ludgate Hill · London EC4M 7JN UK
Phone: +44 203 887 6132

ehlers-danlos.com | info@ehlers-danlos.com

HYPERMOBILITY PLENARY SESSSION and Q&A (TRANSCRIPT)

2017 EDS Global Learning Conference
September 8, 2017

Howard Levy, MD, PhD
"hEDS in Adults"

Antonie Kline, MD
"Hypermobility in Children"

Clair Francomano, MD, PhD
"Hypermobility Spectrum Disorders"

Lara Bloom (Q&A)

Video https://youtu.be/bge1bsQUAx8
Slides ehlers-danlos.com/2017-eds-global-conference/

H. Levy Hi, I'm Howard Levy, and I haven't had my coffee yet, so that's why I'm moving a little slowly this morning. So, I'm here to talk to you about hypermobile EDS, and this is a CME conference so I have no financial disclosures or any other conflicts to declare to you.

When Lara contacted me a while back and invited me to come talk about hEDS, I wrote back and I asked, "Okay, I got 30 minutes. Do you want me to talk more about the new diagnostic criteria or on the management?" I think the problem is that this whole US-England thing. Common language, but we don't really speak the same language – so her answer was, "Yes." I'm not sure I can do all of that in 30 minutes, but I thought I should probably focus primarily on the diagnostic criteria, because they have generated, maybe, a little discussion or controversy and, maybe, one or two people are not totally pleased with it. So, let's go into that in a little more detail, and you don't have to be super nice to me. I've developed a thick skin and I like vegetables, so if they're not rotten when you throw them at me, you know, I can collect them!

Why did we do this? It was not only to hopefully shorten your diagnostic odyssey and to get you through diagnosis quicker, it was really because we wanted to enable this wonderful project that Christina and Peter are now undertaking, to hopefully find, they said, the gene – or some people have said the gene. Frankly, I think it's the genes – but to better understand what the heck is this condition, and the problem, most of us think, one of the main problems as to why this seems to be an orphan genetic condition for which we don't know the genetic cause, is that it is not one condition. And when you collect a huge pot of people who look somewhat similar but are actually different, and ask what do they all have in common that causes their problem, the answer will be nothing, because they're not actually all the same. We call that genetic heterogeneity.

So, yesterday Professor Rodney Grahame told you that the prior criteria were more inclusive rather than exclusive, and we – or I should say I and at least some of us on the committee – very intentionally tried to make these new criteria more exclusive or tighter. Tight and lax, not meant to be a pun, but appropriate in this group. And the purpose of being tighter is to have a higher bar, to say, people who have exceeded this bar, we believe, are more likely to all have the same thing. Frankly, I'm not at all convinced that we've succeeded in that, but at least I think we will have cut down the variability of what goes into people who get over that threshold. So, again, this is just a first step. We might need to make it tighter yet, or maybe we've made it tight enough that powerful, statistical genetic tools will enable colleagues doing these types of research projects to figure out what are the genes involved.

That was one reason. Another reason is, actually, it's to your benefit to not only have a diagnosis but to have the correct diagnosis because your management might be different if you have a different condition. There are actually some conditions that masquerade as Ehlers-Danlos syndrome — a genetic word for that would be phenocopy — but some of those other conditions actually have a cure or a targeted treatment. And, as most of you probably have figured out by now, we don't really have any targeted treatment specifically for EDS. So, in reality, in some ways, you're better off not having Ehlers-Danlos syndrome. So, sometimes it's just inappropriate to just end that diagnostic journey prematurely. Sometimes it's better to keep looking until you find the right diagnosis, rather than stopping when you have a diagnosis.

For those of you who are still angry, upset, frustrated, or just concerned about the new criteria and concerned that you might lose your label of Ehlers-Danlos syndrome — I encourage you to ask yourself, calmly when it's not laden, ask yourself what you need. Do you need an EDS diagnosis, or do you need a diagnosis? And if you need an EDS diagnosis, ask yourself why. Maybe there's a legitimate reason, but maybe all you need is a label that sets you apart and says, "You ain't normal, but maybe, sometimes, you don't know quite what it is that's not normal." Maybe you just need a diagnosis rather than an EDS diagnosis — and then beyond enabling those of us in the EDS community to do better science, and supporting all of you in getting something closer to the correct diagnosis and the correct care, there's the matter of everybody else out there.

Raise your hand if anyone has disbelieved that you have something wrong with you, be it a family member, a friend, or another healthcare provider. Part of the problem is a lack of credibility. Right? If we just have this label hEDS and throw everybody with pain, or everybody who has ever had a subluxation into that bucket, then it becomes a meaningless phrase that everyone else just sort of rolls their eyes at and says, "Oh, there goes another complainer with a bunch of pain and other problems." That ain't helping nobody. Alright? So, we need to move away from that. Those are just some of the major reasons why we had to undertake this revision. It's not meant to be perfect. It's meant to be a step forward.

So, what did we do? We prioritized specificity over sensitivity. In English, that means some people who probably do have EDS may be falsely or incorrectly excluded. We have sacrificed sensitivity in order to reduce the false positives, in order to reduce falsely including people who actually don't have EDS — false positives. Reducing false positives is moving towards specificity. Maximizing true inclusions would be sensitivity. So, that left the problem of, what do we do with folks who no longer meet

the current criteria, but ain't right and need a diagnosis? And that was the genesis of the phrase hypermobility spectrum disorder.

Lara already told you about how much time we all invested. We invested a lot of time agonizing over the name for HSD, and Rodney already started picking apart the name yesterday, very appropriately so; but, my simplified way of explaining this to you is we needed a name that didn't sound remotely like Ehlers-Danlos syndrome and didn't sound remotely like joint hypermobility syndrome, because we wanted to minimize confusion with older terminology and new terminology. We wanted to get something that had not been in the literature before, that didn't look so similar to something literature- that your friends, and your colleagues, and your other healthcare providers would say, "Well, that's just the same thing with a slightly different name." It's not. It's a new diagnostic term that's meant to satisfy your need for a diagnosis, while at the same time recognizing that we big-headed, ivory-towered clinicians and researchers still don't know what the heck it is.

So, there's HSD. Yes, it needs a lot more work to better define it and pull it apart, and eventually, relabel people who are getting that label currently. So, as we learn what the genes are involved in hypermobile EDS, as we learn more about what's going on in people that are currently going to get labeled with HSD, the intention is that some of those people who are this year going to get diagnosed with HSD, will get re-classified and, in fact, have some form of Ehlers-Danlos in the future once we have a better idea of what we mean when we say hypermobile EDS — and some of you will not. Some of you will have something else that will require additional ongoing research to try to figure it out.

Rodney spent a lot of time yesterday very appropriately talking about what we did not include. That is a great source of frustration, I would wager, the biggest source of frustration for many folks about the new criteria. I wanted to spend a little time on why they're excluded, and the point really here is not to say that these are not features of Ehlers-Danlos syndrome, but rather that they are not specific enough to distinguish an EDS patient from somebody else. Can you think of any other medical problems, or psychological problems, or just stress that cause sleep disturbance or fatigue? I hope so. I certainly can. Can you think of other conditions, I can, that cause POTS and GI disorders and dysautonomia? Absolutely, probably dozens of them. Anxiety and depression are probably the most common thing in all of medical care.

In addition to being a geneticist, I am also a primary care doctor. What they didn't tell me when I went into primary care medicine, that about half of the job is mental health.

It is extraordinarily prevalent. Anxiety and depression are so common, that they're not useful as discriminating factors in trying to distinguish a diagnosis. None of this is to say that they're not part of the condition, simply that they lack the specificity to say this person with these conditions has EDS, whereas another person with these traits has some other problem. They didn't help with diagnostic specificity.

And then, these last few things, Chiari, tethered cord, mast cell — fascinating questions that have only emerged in recent years, that desperately need more research to figure out are they truly related, in what way are they related, and what is the causality of that relationship. It is one thing to say that things co-occur. It's quite another to figure out which one caused the other. If you stand at an intersection and see a light turn from green to yellow to red, you will see the cars slow down and come to a stop. Did the change in color of the light make the car stop, or did the car slowing down change the color of the light? The answer is neither. Right? The light told the driver to slow the car down, but if you don't intuitively understand that, you could, if you'd never seen a car or traffic light before, you could conclude, erroneously, that the car slowing down made the light change, or that the light changing color automatically slowed the car down. And, maybe, with self-driving cars, we'll get to that point, but we're not there today. So, the difference between association and causation is another really important scientific principle.

I probably spent too much time on this slide. The key points are, we wanted things that really were clearly associated with Ehlers-Danlos syndrome and clearly distinguished EDS from something else. They're not; none of the writings were meant to say these aren't part of EDS, just that we're not proposing them as diagnostic criteria. So, with that out of the way, what did we do to say, okay, how are we going to diagnose EDS? We went back to basics, and we said, okay, Ehlers-Danlos syndrome is a heritable connective tissue disorder, and we picked apart those words. And that's just simply defined on the slide here: heritable means you expect a positive family history. Connective tissue means we should see some generalized joint hypermobility and some other systemic connective tissue involvement. And the word disorder is meant to imply that it goes beyond just the connective tissue but has some consequence. In this case, we felt most comfortable saying functional musculoskeletal consequences. And then, from there we went on to, okay, how do we actually measure those specific definitions?

Sorry, I've jumped ahead of myself. What we've established for the criteria were these three things on the slide here. So, we've put the elements from those definitions- family history, hypermobility, connective tissue involvement, musculoskeletal

consequences. We've put those into the rubric that you've hopefully seen by now in the paper or in the checklist. You have to have all three of the connective tissue manifestation of generalized joint hypermobility. You have to have at least two of the three that cover those three categories, again, systemic connective tissue, heritable (meaning positive family history), and disorder of musculoskeletal complications. And then, the third criterion is, it can't be something else that might be a phenocopy, that might look like these features, but actually already be diagnosable, if not yet diagnosed, as something else.

For those who haven't seen it, if you go to the EDS Society website, this link brings you to a checklist that makes it easy to fill and score yourself, or if you're a clinician, score a patient for the condition. A screenshot of the first criterion from the checklist and from our paper: how are we going to measure generalized joint hypermobility? As you were told yesterday, for better or worse, we've gone with the primacy, if you will, as Rodney did, of the Beighton score. We hedged a little bit and put in here the five-point questionnaire. The reason those were chosen is because the working group on measuring joint hypermobility identified these as the best two tools out there currently for measuring joint hypermobility. But the main finding of that committee was, there isn't a good tool. These are the best two, but there isn't a good one.

So, our goal was to be as standardized and strict as possible, and there are details about meeting all of the criteria in this checklist. So, don't look just at the checklist and in the paper. Please read it carefully. Look at the figure that discusses the Beighton score and look at all the footnotes, because that's where the details are that help to try to make this, I want to say, more objective. Our goal was to create a scoring system that any clinician could use, and I don't think we've achieved that, but we're trying to move as far away from purely subjective things as we can. What does it mean to say soft skin? What does it mean to say stretchy skin? Those can be hard things to measure. We are trying to get as close as we can to something objective and measurable to reduce that genetic heterogeneity problem. That problem of people being labeled with hEDS, when, in fact, they might have something else.

Criteria for how to perform the Beighton score are important, and we've gone a little above and beyond what was in Peter Beighton's original paper. Again, trying to be more standardized. So, positioning of the hand and arm when checking for fifth finger hyperextension, and when pulling the pinky back, we've agreed that the measurement should only be at the joint where the pinky joins the hand, right there. So, we're not including did the tip of the pinky get behind the knuckle? We're only looking for 90 degrees at that one joint, much stricter criteria, intentionally. With

the thumb to the forearm, that one's pretty straightforward. With the elbow and the knee, it needs to be greater than 10 degrees, not 10 degrees or more, greater than 10 degrees. Ideally — I've been standing on this soapbox for years — ideally, this should be measured with a goniometer. Many people don't. Many clinicians don't. I regret that.

There have been a few papers published, not as many as I think need to be, and they sort of suggest that some experts are pretty good at eyeballing it. But that is experts, and they're pretty good, but not perfect. People who don't do this routinely — frankly, I surprise myself sometimes that I'm examining a patient and I'll look at that elbow and I'll go, "Oh, that's going to be positive." I measure it out, and it's not. Or, conversely, I look and I go, "That's going to be negative." It measures out to 12 degrees. So, I urge people to actually measure, and if you've been evaluated by someone who did not measure the joint angle, then I would suggest to you that four of your Beighton score points may be in question. Maybe, not necessarily, but maybe. And then, the fifth one, everybody can get their palms to the floor and their feet flat. I'll do it for you now. That's not positive. Okay?

So, there's some criteria. If you spread your feet far wide, you're closer to the floor. Right? So, they need to be close together. It has to be palms all the way flat, not just the fingers. Alright? Strict criteria. We're trying to figure out who really does and does not have this condition. Standardized and strict, and then how to interpret a Beighton score. That was just how to determine how many points out of nine there are, and then what do we with the score. So, Peter Beighton's original paper said you need a score of 5; and it is widely recognized and has been for a long time, that joint mobility changes over time, changes with trauma, and changes with a bunch of other things. How do we adjust for that? The short answer is, we're guessing. We're guessing. But, what we've proposed is, if you're younger than puberty, we will take a score of 5, rather than 6, because we know that children are looser than adults. If you're between puberty and about age 50, we're going to go with the standard 5-point threshold, and if you're beyond age 50, then we're going to be more lax and say a score of 4 is good enough.

We're guessing. What do you do with a 2-year-old, a 5-year-old, an 8-year-old? Is 6 high enough, or does it need to be higher? And puberty doesn't happen overnight, regrettably. I don't want to relive mine. So, what if someone's right in puberty? And what's magic about age 50? I'm beyond age 50. I did not feel that different. I felt a little hungover the next day, but otherwise, I did not feel that different. Right? So, if you're 49 and 350 days, is that different than 50 and 5 days? It's an arbitrary cutoff, and we're going to still have some ambiguity and uncertainty for people in their 40s. We don't know for sure. We had to choose something, so that's what we're starting with.

And then, the five-point questionnaire — well, actually, I should go back to my first point here. Rodney spent a lot of time yesterday, and I agree with him, pointing out that the Beighton score only looks at limited joints. We know that, and I think most of us clinicians who have been in this field for years, have always done a subjective joint exam as well, and factor that into our clinical assessment as to whether or not this is Ehlers-Danlos syndrome. And I think we still need to be doing that, but the problem is, how do you standardize it? How do you teach that to others? How do you get agreement?

I learned much of what I know and do today from Clair, and Clair and I often disagree on people's joint laxity and skin softness and skin stretchiness. So, the mentor and the mentee, we all do things differently. That's just human nature. So, we needed something that we could standardize, and the agreement among the committee was, well, we agree that subjective joint exam is critically important. We don't know how to factor it into the criteria. So, it is just left out there as needing more improvement, as was discussed yesterday. And then, as I told you earlier, the committee found that the five-point questionnaire is the next best thing. So, again, just to make something standardized that anyone could apply, we said, alright, if you miss by one point on Beighton, then turn to the five PQ to see if that changes the assessment. But that's far from perfect as well, and the studies have shown that it's 80-90% specific, meaning 10-20% of people who have a positive five PQ, actually don't really have joint laxity. So, it's good, but it's not great. It hasn't been validated for use in children. Bottom line, as you've heard many times, we need better assessment tools.

On to systemic connective tissue manifestations, which are three separate features within criterion II. I have 10 minutes left. Wow, I am going slower than I thought I would! There are 12 elements here. The checklist doesn't include any of the footnotes, so I want to emphasize the footnotes. It has to be unusually soft or velvety skin, not just, "Yeah, that feels a little soft." And if you just put on moisturizer your skin will be softer. This is a subjective examination. There is no way to standardize it, but we recommend having a high threshold. Skin hyperextensibility: Rodney has published wonderful work on skin stretchability. He has a very cool assessment that he calls the rubber glove test, which I'm still trying to get confident learning and applying myself, but how do you teach that to others? So, what we agreed upon, just to have something measurable, is to look on the forearm between the wrist and the elbow, tug the skin, and if it goes between 1.5 and 2 centimeters, call that positive. Back of the hand, measuring distance that the skin stretches isn't helpful because that's not all stretch. Some of that is normal extra skin. If you couldn't pinch skin on the back of your hand, you'd never be able to make a fist. If you couldn't pull skin on the back of your elbow, you'd never be able to bend your elbow.

Be grateful that there's some stretchy skin there, and notice that when you make a fist or bend your elbow, the skin doesn't stretch as far because that's not stretch. That's extra skin to allow your joints to move. Stretch marks need to be unexplained. So, if you're female and past puberty it doesn't count because, I'm sorry, but at puberty, and especially women, stretch marks develop. And there has to not have been a significant gain or loss of weight because we know that causes stretch marks.

Abdominal hernias: we exclude hiatal hernia. The hiatus is the opening in your diaphragm through which your esophagus and some nerves and blood vessels pass. If you didn't have a hiatus, you never would have been born. Technology for measuring things is now much better than physiology for creating things. Everybody has at least a little bit of extra space between the things that run through the hiatus and the ring that is the hiatus. Everybody has some degree of hiatal hernia. For most of us it's trivial, for some of us it's extraordinarily severe and causes major problems, but because everyone has it to some degree, and we couldn't find a good way to standardize it, we left hiatal hernia out of hernia for this criteria.

Scarring: there are pictures here to look at. We've moved things that – the poor people with what was originally type II EDS and then mild classical EDS, I feel regretful that we are still not helping you very much. You keep bouncing back and forth. You were originally in the type III – well, you would fall between we're not sure if it's type II or III – and then we said, "Okay, if you've got the skin findings it's classical, but mild classical." And I think we are sort of walking that back a little bit now, and we are acknowledging that some of the skin findings can be seen in hypermobile. So, we're still bouncing back and forth, but as you can see in these pictures, the skin findings in classic EDS are much more severe.

Pelvic prolapse: again, it needs to be unexplained. So, once you've had pregnancy, that changes the structure of the pelvic floor. That increases the risk of pelvic prolapse, and that makes this not countable towards the diagnosis. The oral cavity, it's dental crowding and a high or narrow palate, not one or the other. It has to be both. Again, we're going for a higher threshold. But we do include historic, alright? So, if you've had extractions and a palate expander and braces, we'll count that for crowding. Again, total of 12, possibly need 5 or more. This ain't perfect. If you're reading the paper click the little blue hyperlinks for the footnotes after each paragraph and that's where you'll see the details that I've highlighted here. And, again, like with measuring joint hypermobility, we need to get better at this once we have a better idea of what the genes are and have some gold-standard test.

The other two pieces of criterion II are positive family history and the additional systemic manifestations. Family history needs to be a first-degree relative, and that's because we share 50% of our DNA with our first-degree relatives. You get out beyond that and there's less DNA shared, and we have less confidence that you really were likely to have inherited it. That family history has to be the current criteria. If you just take a bunch of people in a family who say they have loose joints — if you count one person's loose joints to make the other's EDS diagnosis, and then that person's loose joints to make the others EDS diagnosis, no one ever independently fully met the criteria and you could deceive yourself into thinking it's hypermobile EDS, when it's really something else. So, it really has to be hypermobile EDS, not a prior diagnosis of we think it's hypermobile EDS and not HSD. Yes, it's a strict criterion, intentionally so for the benefits of better science. Again, the bottom line here is that there are lots of things that cause loose joints. They're not all EDS.

Musculoskeletal complications, daily pain, or chronic widespread pain: I still puzzle why we separated those out. I think they're almost identical, but there are some subtle differences. And then, dislocations or instability, there are some definitions. You need to have multiple, not just one. And if it's instability, ideally, it needs to be a medical provider who confirmed that it really is instability at multiple sites. Trauma excludes it. If you've injured a joint, dislocated it or just predisposed it to dislocation, that doesn't count. That doesn't count because trauma destabilizes joints. And dislocation has a definition, it's a bone being out of position that has to get put back in. So, you may feel as though something is unstable and moving around, but that may not meet the medical definition of an unstable joint or dislocated joint.

Finally, excluding other diagnoses: skin fragility, if it's severe, should suggest another type of EDS. Most importantly, think about other conditions that could explain some of the findings; and here is a very controversial one. What we've agreed upon in these criteria, is that if you have an autoimmune connective tissue disorder that destroys your otherwise normal connective tissue, like rheumatoid arthritis, psoriatic arthritis, lupus, things like that: that causes pain. That causes joint instability. So, in criterion II, if you've got one of these autoimmune rheumatologic conditions, we don't count that third piece of criterion II, the pain or instability, because your autoimmune disease might have caused that. So, in order to meet criterion II, if you've got one of these autoimmune conditions, you've got to have the family history and 5 of the 12 systemic manifestations.

We know that's a high bar. We know it's going to be hard to meet, and we know we're probably going to incorrectly exclude some people with rheumatologic conditions

who happened to also have EDS. We know that. It's unfortunate, but again, it's in the goal of trying to get better at deciding what actually is the genetic cause of this condition. Then other conditions that can cause loose joints, poor muscle tone, and nerve and muscle problems can also cause joints to be loose and there are a lot of people walking around with nerve and muscle disease who have loose joints, who look like they have EDS but, in fact, have something else. So, if there's something in that category, that changes it.

I want to show you the data that I extracted from reviewing my charts. I looked at patients that I saw from March 1st this year through last week, and I did the same time period in 2015 and 2016. And what you can see here — I'm assuming at least one or two people in this room are red-green colorblind. This quadrant down here is green, and I am hoping you can tell that it's different from this orange here, and that you can tell that the orange is different from the yellow. Anyway, in 2015 approximately half of the people that I saw, I thought had a connective tissue problem. About 40% of the group I thought had EDS, and about 10% of the group I thought had something that wasn't EDS, but similar connective tissue. A couple people had other specific connective tissue problems like Stickler syndrome, or something else. In 2016 I didn't have any of the other conditions but, again, it was 50-50 not heritable connective tissue, or yes, a connective tissue. In that case, 25% total I called EDS and 25% I said, not EDS but something else in the spectrum.

This year it's now only one-third where I said, "You don't have something in the spectrum." And, again, these are small numbers, so this may not be a true change from the criteria, but the biggest change, I think, is that I've labeled a lot more people with HSD than I had in prior years. This 30% EDS, I don't think it's statistically going to be any different from the prior two years. Now, the next thing I did is I took my 2015 and 2016 data and pulled them. Those are now all together in this pie, and it's still about half not connective tissue and half is connective tissue. The biggest change, of course, is that the people that I had previously labeled as not EDS but something connective tissue, now if I try to reapply the new criteria to the old patients, which is risky because I wasn't asking the same questions and doing the exam exactly the same way, but with that understanding that it's risky to do that, most of those people are now relabeled as HSD. I would now give a specific named condition to those people, where in the past I said, "You got something, but I don't know what it is."

If you pull apart what goes into each of those pieces of the pie — the people that I've labeled with EDS and the old criteria — 91% I said had hypermobile and 9% classical. A few of them lost the hEDS diagnosis when I redid the analysis and I moved them to

HSD. So, some people would actually move from EDS to HSD, a couple people moved from classical to hypermobile because their skin findings were not as severe. These are people that I doubt would have a type V collagen mutation. No one had HSD before. Everyone who had HSD before, all of them got moved to hEDS, and there was actually one person who I had previously labeled with hEDS, but with the new criteria, the correct diagnosis would be psoriatic arthritis and no longer meeting criteria.

In those who I now label with HSD, of course, none of them had it in the prior nomenclature because it didn't exist; 71% of the group that I called "not EDS." I'm out of time. What did I want to highlight? I wanted to highlight that a couple people who I previously thought had something, now I'm uncertain that they didn't get labeled at all. And then the people that didn't have anything connective tissue, these are the diagnoses that were most common: some autoimmune rheumatologic, a fair amount of mitochondrial neurologic disease, some arthritis, and spinal stenosis, but half of them I couldn't tell what they had. They just had pain. I didn't have a diagnosis. There are a bunch more slides here about the manifestations of EDS. It's all in the paper. You have my slides, and this all emphasizes that hEDS is a lot more than the diagnostic criteria, to reassure you that we did intentionally include all this as part of EDS. It just wasn't good enough to be part of the diagnostic criteria.

Sure enough, I told Lara that I thought it would be hard, and I told you that it would be hard to get to management. So, I predicted I'd be way over time and I am. So, it's all in the papers and you'll have these slides, and I'm happy to talk more about it when we have more time. Thank you for your attention.

T. Kline Good morning. I want to thank you for inviting me to speak today about Ehlers-Danlos syndrome. And I'm sorry Brad Tinkle couldn't be here, and his shoes are very large to fill, so bear with me. I am Tonie Kline. I'm a pediatric geneticist at Greater Baltimore Medical Center, and, as you know, we have the EDNF Center for Clinical Care and Research there. So, this information is from my practice at GBMC. Today I'm going to, hopefully in the time allotted, do a brief overview of hypermobile EDS and the new criteria – but that has been very recently discussed – talk about some presenting symptoms and signs that we see in the practice, and some management recommendations.

We'll start with the overview. As you've also just heard, everybody knows that EDS is a hereditary disorder of connective tissue, most due to defects in collagen and most have skin involvement, and joint laxity, and there can be involvement of the cardiovascular system, as well as other systems. It certainly can be progressive and unpredictable. It's

extremely common, and most types are autosomal dominant, meaning that if you have it, you have a 50% chance of passing it on with each pregnancy.

So, you've heard several times about the new criteria, which were committee driven, and that the major requirements include hypermobility, and then two of systemic or musculoskeletal involvement or family history. From my point of view, the pediatric population is different from the adult population. For example, parents and children mean different things. The parent says, "We're going green."

"You mean like broccoli and stuff?"

And most children are very different from each other, such as this girl and this boy. So, the diagnosis of genetic conditions in children is different than in adults. And this says, "I'm sorry, Jimmy. But the results of your test show that you're not allergic to vegetables."

For the new hypermobile EDS criteria, this is how we perceive it in pediatrics. But, we certainly recognize that it was based more on adults than in children, and it needs to be very strict in order to help find the gene or genes. So, if you think about the three major requirements, in children, for hypermobility, the score has to be higher as Dr. Levy just said, if the children are prepubertal. For the systemic signs, many may not yet have been developed, or might not be to the maximum required, and I'll show you that. For the musculoskeletal signs, many joints may not yet be involved, but the criteria are pretty much the same and family history is the same.

The Beighton score is based on exam of some major joints, as we've heard. You get one point for each item. So, as Dr. Levy just said, the Beighton score has to be at least five post-puberty, and at least six pre-puberty. Here are some examples of the maneuvers, and here is the worksheet that we used with the extra points from the five-question questionnaire. So, one of those points is tricks with joints. Here's just a little montage of some tricks with joints that we've seen in the clinic.

If we move to the systemic signs, some are easier to find in children: unusually soft velvety skin, unexplained stretch marks, and dental crowding with high, narrow palate, are fairly straightforward. You can see stretch marks here, and here, and the high palate. Some are difficult to reach full requirement in children, in my opinion. The skin hyperextensibility, it's difficult to get 1.5 cm, especially on a tiny little kid. To get bilateral piezogenic papules and two or more atrophic scars, often we see just one foot having piezogenic papules or just one scar on a child. It's not to say they won't

develop it, but at that moment in time, they don't have it. Some of the systemic signs are much less common and less likely in EDS. For example, long arms, long fingers, and recurring hernias, you might see in some other connective tissue disorders. And some are quite rare in children, such as the prolapse, including mitral valve prolapse and aortic dilatation.

Overall, it's very difficult to get to a systemic score of five or more. Since the new criteria have been put in place, over 50% of the individuals that I previously would've considered hypermobile EDS are now hypermobility spectrum disorder. Moving on to presenting symptoms and signs in the clinic: this is based on a review of 192 patients with Ehlers-Danlos syndrome, in which the female to male ratio is about 2:1. Most of them have included individuals with hypermobile EDS, about 85%, with the rest mostly classical in 15%. The age range has included children from 7 months of age to 21 years, but most of the time we see children 5 years or greater. Most of the individuals have been white, but there are individuals of all races and ethnicity seen.

Most referrals have been made by pediatricians, but then orthopedists and other specialists such as neurologists have been included. About two-thirds of the time they've been referred for hypermobility or to rule out EDS, but other connective tissue disorders have been also the cause. So, this is a list of the most common presenting symptoms of the children that I see in the clinic: pain in more than one joint, recurrent pain in a single joint, excessive pain after injuring a joint, hypermobility of joints, frequent subluxations (joints that come out of where they're supposed to be, but go back in without assistance), several dislocations that Dr. Levy just described, and then dizziness and/or fatigue. In terms of musculoskeletal complications, we see pain in joints, we see flexible joints. You can see a picture of a very — hands from a single individual who is quite flexible here. Easily dislocated joints, about one-third of the individuals, and then fractures, relatively common, about 18%.

We also see flat feet, as you can see on the bottom of the slide. In addition to flat feet, we often see inward turning of the ankles, the tricks with the joints that I also showed you before, and hypermobility. Here are some other joints that appear hypermobile as also have been discussed. Skin findings include stretchy skin and ears, sometimes more common in the classical group. *Cutis marmorata* is the lacy mottled appearance of the skin, as you can see on this individual, soft velvety skin, and visible veins. I think you can see the veins on this boy's chest. Also, unusual scars in about 33%; stretchmarks, here are some on the back of a boy, and easy bruising is very common as well. Piezogenic papules, we already discussed. We also see winged scapulae, scoliosis, and sometimes *pectus excavatum*, which is the in-turning of the chest bone.

In terms of the GI system, many children do present with frequent abdominal pain. In addition, about 16% will have constipation, but also many will have recurring diarrhea. There also are complaints of nausea or vomiting and poor bowel motility is probably more frequent than we even realize. We had recorded about 21%, but most of them have not had motility studies; 6% present with gastroesophageal reflux, and 4% with mast cell dysfunction. In terms of the cardiac system, many children complain of dizziness, especially when standing up, frequent lightheadedness, feeling faint particularly when standing in place for a long time, and several children have actually fainted. We only found about 3% of our group to have dilatation of the aortic root, and this is a diagram showing the aorta as it comes out the heart and this is the area in which it's concerning that it could be dilated before it comes down and gives the rest of the body oxygen.

This condition, dilation of the aortic root, is certainly repairable, and you want to repair it because complications can occur. One recent study showed that there was an increased size of the aortic root in about 3% of children but rarely dilated further after 15 years of age. In addition, the valves inside the heart are at risk, and mitral valve prolapse we only saw in less than 2% of our group. Postural orthostatic tachycardia syndrome (POTS) was seen in only about 13% of our group, although many children complain of dizziness and symptoms of orthostasis include dizziness, lightheadedness, weakness, change in vision, palpitations. There is a strict definition of POTS, usually, depending on the age of the child, an increase in the heart rate by 30 (or 40 bpm if the children are younger) within 10 minutes of standing up, or for children under 13 a heart rate above 130 by itself.

As we heard yesterday, if the children are symptomatic with this and they don't meet the strict criteria, sometimes management can be extremely helpful. Only 0.2% of our group reported dysautonomia specifically. For neurologic complaints- frequent fatigue, brain fog in the older children, confusion, sometimes, decreased energy, and need for increased sleep; 12% have had hypotonia, particularly when they're younger, and then about 20% complain of headaches, 12% migraines. So, these are pretty common. Craniocervical junction abnormality and Chiari are not commonly found in the pediatric population, but both are known to accompany EDS. If there are findings on the neurologic exam and/or headaches, we generally recommend upright brain MRIs and upright cervical spine MRI in flexion and extension, or CT scans, or x-rays. There are centers that have the ability to do upright MRIs, and these are what you should seek out. If there is any concern about any of these, we refer to pediatric neurosurgery.

We do see differences in behavior and development, but it's always unclear if this is in general and is probably unrelated to EDS, but we don't truly know; 14% of our group have ADHD, 13% anxiety, and 7% depression, about 5% have had varying degrees of autism including Asperger, and then about 12% have had intellectual disability or specific motor or speech delays, and about 4% specific learning disabilities. So, in terms of management, for the joints, we do recommend curtailing high-impact aerobic sports, and we always highly recommend swimming in particular, but also other lower-impact sports or exercises. We do recommend physical therapy for core strength and limbs, especially if there's a more acute finding with a specific joint, and sometimes warm water physical therapy can be extremely helpful.

Patients report that myofascial trigger point massage is helpful, and we do recommend support for some painful joints, but never total immobilization. And then, of course, we recommend non-steroidal anti-inflammatory drugs such as Motrin or ibuprofen, primarily. In terms of the feet and legs, in addition to physical therapy, sometimes foot support such as ankle-foot orthoses can be helpful if there's flat feet- and always continue exercising. We think that strengthening the muscles will always help the joints because there will be less pressure on them. For the upper extremities- sometimes splints for acute issues can be helpful, and the occupational therapist can help provide pen or pencil accommodations. Some children will benefit from ring splints, particularly if they're using their fingers a lot for a musical instrument or something like that.

Regarding school, modified physical education is always helpful and we encourage, if the children are old enough to do self-regulation – like the child would know that tug-of-war or rope climbing would not be helpful for loose shoulders, or something like that. The 504 plans that you can obtain from the school system are very helpful, particularly if the child needs to miss school days and have that sorted out, so they don't get behind. Other accommodations such as a wheeling backpack and being able to use water bottles in school, sometimes need a note specifically saying this. Sometimes children will need a wheelchair, this occurred in about 3% of our group, but often we'll then see the child later with some of the other recommendations and they haven't needed the wheelchair, which is always exciting.

For pain management, it really is not very well studied in pediatrics. Overall recommendations include primarily physical therapy, especially the warm water, regular strengthening of muscles, as I said, minimizing the contact sports, and encouraging swimming as a life-long sport. We highly recommend Epsom salts, either in the bath or foot soaks, or even added to the shower if you put the plug for

the drain in while you're taking the shower. This will help bring magnesium into the cells, which definitely alleviates pain, and then the myofascial trigger point release. We do, at times, refer to rehab physicians or pain clinics depending on the presentation of the child. And then for medications, as I said, analgesics, which also can include Tylenol. We never recommend narcotics in the pediatric age group. We consider a topical approach such as topical lidocaine for localized areas or topical indomethacin, diclofenac, and we don't usually recommend compound creams below the age of 15 because of some of the components.

Again, the accommodations in school, sometimes handicapped parking passes can be helpful, especially for large areas like malls, and just to be sensible about knowing what your body can do and can't do. For the heart, we do recommend all children to have an echocardiogram, as was mentioned yesterday. Findings in the heart are now part of the diagnostic criteria. We tend to repeat this in 3-5 years if it's normal, really until the late teens, and refer to pediatric cardiology if there's an abnormality. For POTS, we recommend lots of hydration with electrolytes, such as the Nuun tablets, is one brand, but there are other tablets and they can found in health food or Whole Foods stores, rising up slowly whenever you do have to get up, and considering the use of compression stockings even in children, as well as exercise.

From the GI point of view, for constipation and bowel motility, you can consider some medications. If there's a question of motility, a gastric emptying study can be helpful, and referral to pediatric GI if there are major issues. For mast cell dysfunction, as was mentioned yesterday, a tryptase level can be obtained at the time of an involvement or outbreak. Often these are normal; however. Consider eliminating histamines from the diet and/or identifying a trigger and eliminating that, medications if indicated, and referral to pediatric immunology if severe. These individuals are few and far between, unfortunately.

For the Chiari malformation and craniocervical instability, sometimes a hard cervical collar can be helpful, as can traction. Sometimes cervical decompression will provide the neurologic improvement, but this is a drastic step, so we definitely proceed cautiously. For the fatigue and the poor sleep, we highly recommend regular bedtimes, not recommend to oversleep, generally, recommend no caffeine- and there are special pillows that can be ordered that can be wedged in various ways under the neck or the shoulder to help get the child most comfortable for sleep. And then, for behavior management, always validate that the pain and the symptoms are real, which sometimes extended family and schools will be dubious about, to provide supportive reassurance for the child through the family, to obtain the school

accommodations. Sometimes we'll have to write letters. There are letters on the EDS website as well. We recommend considering family counseling and/or behavioral counseling if this is an issue, particularly if anxiety or depression are present- and then, mindfulness-based stress reduction, including things like yoga and meditation, can be extremely helpful.

I just wanted to mention some current studies, as you've heard, of the search for the genetic cause of hypermobile EDS, is ongoing. Dr. Francomano has had an ongoing evaluation to assess mitochondrial function. We think that the fatigue can have a mitochondrial component and this ongoing through Children's Hospital of Philadelphia and our center. And then, we have been involved in a study with Johns Hopkins Hospital to assess the quality of life in the pediatric population in those children with non-vascular EDS. So, if you've received a request to participate in one of these questionnaires, we encourage you to try and do this, because the more information we can get, the better for all of us. We're all in this together and I think that's probably one of the themes of this meeting.

I'd like to thank Clair Francomano for being my colleague, and friend, and leader through this study, the two genetic counselors that work the most with the EDS patients, Marsha Ferguson and Amy Kimble, my hospital Greater Baltimore Medical Center, and the EDS Society, and all of the families. Thank you very much.

C. Francomano It's really great to be with all of you today. I'm Clair Francomano, and my charge is to talk, today, about the hypermobility spectrum disorders. So, I am a really a stand-in today for the hypermobility disorders committee, headed by Marco Castori, but also including Brad Tinkle, Howard Levy, Rodney Grahame, Fransiska Malfait, and Alan Hakim. I'm going to use the paper that they published in *The American Journal of Medical Genetics* last March as the framework for my presentation.

I have no conflicts of interest to disclose for the purposes of CME. This is the paper about the framework for classification of joint hypermobility and related conditions. As you heard from Dr. Levy, it was really necessary to give some very careful thought about how do we really present the information related to joint hypermobility in the context of these new diagnostic criteria for hypermobile Ehlers-Danlos syndrome. I have to commend the committee because they really, they labored very, very hard over this. All of them recognize that this is not a perfect solution and all of us recognize it's not a perfect solution, but it is a step forward. I hope by the time I finish today you'll have some understanding of some of the rationale that went into this classification.

So, just a brief history of joint hypermobility and hypermobile Ehlers-Danlos syndrome: this is summarizing that very, very elegant presentation that you heard from Dr. Rodney Grahame yesterday in less than two seconds. We had the geneticists who've been calling certain features of hypermobility, hypermobile Ehlers-Danlos Syndrome, for many, many years, we were using the Villefranche criteria and this was quite a loose definition of hypermobile Ehlers-Danlos syndrome. The rheumatologists were talking about joint hypermobility syndrome, and in 2009 Brad Tinkle and colleagues publish that probably these two things were the same thing. Castori and his colleagues published in 2014 that they agreed with Tinkle *et al.*, because they had a family where there were people who had been diagnosed, some people with hypermobile Ehlers-Danlos syndrome, some people with joint hypermobility syndrome, and it seemed to be inherited. These two diagnoses seemed to be inherited as a single autosomal dominant phenotype.

Fast-forward to 2017, and we have this discussion by Castori and his colleagues thinking about this framework for the classification of joint hypermobility and, of course, the new diagnostic criteria for hypermobile Ehlers-Danlos syndrome. I'm going to quote from this paper, from the 2017 paper in which they said, "The delineation of a single entity arising as the full-blown expression of the phenotype in common between Ehlers-Danlos syndrome of hypermobility type and joint hypermobility syndrome leaves without an identity many individuals with symptomatic joint hypermobility, and/or features of hypermobile EDS who do not meet the stricter criteria incorporated in the new EDS nosology, and the classification of such cases requires resolution."

This was the fundamental motivation for coming up with a new name, as Dr. Levy mentioned, to include individuals with symptomatic joint hypermobility and some features of what we used to call hypermobile Ehlers-Danlos syndrome, but who do not meet the stricter criteria in the new classification. So, the aims of the framework paper, and my aims today in talking with you about this, are to summarize the terminology of joint hypermobility and related disorders, to present the different types of joint hypermobility, the secondary musculoskeletal manifestations, and a simplified categorization of genetic syndromes associated with joint hypermobility, and then to consider the spectrum of secondary musculoskeletal manifestations, and the range of pleiotropic manifestations of syndromes featuring joint hypermobility, noting that the two separate domains only partially overlap.

This word, pleiotropy, I'd just like to spend a minute talking about that, because it plays a very important role in the way this committee thought about these conditions.

Geneticists use the word pleiotropy to describe the multi-system effects of a single gene in a syndrome. A gene has pleiotropic effects, or is said to have pleiotropic effects, if it manifests in more than one organ system. So, the paper: this was figure one in this paper and it discussed there is joint hypermobility, and then there are musculoskeletal manifestations, which may have a common pathogenesis related to the joint hypermobility. These would include things like musculoskeletal, physical traits, disturbed proprioception and muscle weakness, degenerative joint and bone disease, and micro and macro trauma of the joints.

Pleiotropic or systemic manifestations in organ systems other than the musculoskeletal system would include cardiovascular involvement, primary dysmorphisms, like craniofacial involvement, skin, mucosa, and fascia involvement, and the nervous system involvement. The committee really gave very careful thought to this and distinguished carefully between pathogenesis and pleiotropic etiology, and that plays a key role in the way they thought about putting this framework together. The authors gave a rationale for an evolution in our thinking about joint hypermobility. There were three major reasons before this. One is in thinking about the nosology or the classification. They said, "distinguishing pathogenesis in etiology is the background for a classification aimed at identifying more effective scientific, therapeutic and healthcare strategies."

Second rationale, management of joined hypermobility-related musculoskeletal manifestations likely require homogenous rehabilitation treatment, issues shared by the different genetic conditions. So, this means if you have joint hypermobility it doesn't really matter what the cause is. There are going to be treatment strategies that will be common to all of these disorders.

And, finally, as you've heard, the research implications that a clear separation of the joint hypermobility, secondary musculoskeletal manifestations from the primary pleiotropic manifestations of Ehlers-Danlos syndrome, may help in dissecting the intra-familial and inter-individual variability for studies aimed at deciphering its molecular basis. This, we hope and pray, should help us in the research effort to identify the underlying genetic causes.

How do we define joint hypermobility? We recognize this is a term that is universally accepted to define the capability that a joint or a group of joints has to move passably and/or actively beyond the normal limits along physiological axes. Joint hypermobility is a descriptor rather than a diagnosis, and it may exist as an isolated diagnostic finding, but is often a feature of a larger syndromic diagnosis. Other

words that are used in thinking about joint hypermobility would be joint laxity, hypermobility, hyperlaxity. Dr. Levy talked about measuring joint hypermobility, and it is important to use the orthopedic goniometer. This is a very inexpensive tool, less than $10, you can buy it on Amazon. We follow specific procedures and these have been described in the literature and compared the measured range of motion with the normal published parameters.

Now, in the paper, the committee described four different types of joint hypermobility. They used the word localized to describe hypermobility involving a limited number of joints, and they used an arbitrary cutoff of the number five. The term peripheral, to involve primarily the small joints of the hands and feet with absence of large and axial joint involvement. And then, the generalized joint hypermobility, basically, this is meeting the generalized joint hypermobility criteria as laid out in the hypermobile Ehlers-Danlos syndrome diagnostic criteria. We use the word historical joint hypermobility to described a person with a history of joint hypermobility, which is no longer present on examination. So, it was there before, but it's not there now.

The committee also made the point that joint hypermobility is not the same thing as joint instability – that hypermobile joints may be unstable, but joint instability is not a mandatory consequence of joint hypermobility, and certainly not all unstable joints are hypermobile. Then, they presented about secondary manifestations of joint hypermobility. The first thing to recognize is that joint hypermobility may be completely asymptomatic. There are plenty of people who have joint hypermobility who have suffered no consequences from that joint hypermobility. There are though, a series of musculoskeletal symptoms and complications that may be interpreted as secondary manifestations of joint hypermobility. These include trauma, chronic pain, and disturbances of proprioception or understanding – we use that word proprioception to say, "Can we have a sense of where we are in space, where our feet are in space, or where are our hand is placed in space."

This is another quote from the paper; it says, "Occasional and recurrent musculoskeletal pain is a quite common immediate manifestation of joint hypermobility, as the natural consequence of a predisposition to trauma. The development of chronic pain is sometimes a long-term complication of joint hypermobility, and preliminary studies suggest the existence of hyperalgesia or a heightened sense of pain as a possible form of pain sensitization in patients with Ehlers-Danlos syndrome and chronic pain."

There are other musculoskeletal traits that are associated with joint hypermobility, and you heard about some of these from Dr. Levy. They include *pes planus* of the

flexible type, a *valgus* deformity of the hind feet, the *hallux* or big toe and elbow, mild-to-moderate scoliosis, accentuated curves in the spine including the dorsal kyphosis and lumbar lordosis, deformational plagiocephaly, meaning flattening of the skull of the babies lying in the crib too long on one side, and reduction in bone mass, which may also be a pleiotropic genetic effect. That's a question mark as to whether it's just an associated trait or not.

The paper comes to a definition of a syndrome – after all, we do call Ehlers-Danlos syndrome a syndrome. So, the definition of a syndrome is a pattern of anomalies at least one which is morphologic, or present on physical exam, known or thought to be causally or etiologically related. This comes from a paper by Hakim in 2013. Now, Castori's paper makes the point that the presence of joint hypermobility in combination with secondary musculoskeletal anomalies does not suffice for the delineation of a genetic syndrome. So, just because you have joint hypermobility and these other musculoskeletal features that go along with hypermobility, that doesn't suffice to create a syndrome. They proposed that this appellation or naming a syndrome with joint hypermobility should be restricted to genetic conditions featuring joint hypermobility, together with the primary involvement of at least a second tissue or structure. That would include things like the skin involvement in classical Ehlers-Danlos Syndrome and hypermobile Ehlers-Danlos Syndrome. This is that pleiotropic recommendation that I was mentioning earlier.

Also, as Dr. Levy said, there are multiple genetic syndromes associated with joint hypermobility, and we're most familiar with the Ehlers-Danlos syndromes, but many skeletal dysplasias often present with joint hypermobility: Marfan syndrome, Loeys-Dietz. There's a whole category, big, large category of hereditary myopathies that present with joint hypermobility, Down syndrome and other disorders of the chromosomes and many, many others. We need to consider the differential diagnosis, which is very large, whenever we're looking at a person who presents with joint hypermobility in the clinic.

Coming back to the classification of joint hypermobility – recognizing that joint hypermobility may be entirely asymptomatic. We now have new names for asymptomatic joint hypermobility. We're going to call it either localized joint hypermobility, peripheral joint hypermobility, or generalized joint hypermobility, depending on the degree to which the joints are involved. We may have persons with a well-defined syndrome associated with joint hypermobility, and then we name them by the name of that syndrome. Then there are people with symptomatic joint hypermobility who do not meet the diagnostic criteria for any other known hereditary

syndrome associated with joint hypermobility. We now have a name, or a home, for those folks, which we call the hypermobility spectrum disorders.

These are defined as the presence of joint hypermobility, plus one or more secondary musculoskeletal manifestations of joint hypermobility. The overall clinical picture does not meet the diagnostic criteria for any of the syndromes associated with joint hypermobility. This name, the hypermobility spectrum disorder name, is intended as an alternative label for individuals with symptomatic joint hypermobility, symptomatic, who do not have any of the rarer types of Ehlers-Danlos syndrome and do not meet the diagnostic criteria for hypermobile EDS. Also, it was intended to identify discrete subtypes, filling the full gap between asymptomatic joint hypermobility and hypermobile Ehlers-Danlos syndrome. Therefore, hypermobility spectrum disorders: they include generalized hypermobility spectrum disorder for people with generalized hypermobility, localized hypermobility spectrum disorder, peripheral hypermobility spectrum disorder, and historical hypermobility spectrum disorder.

Now, the committee went on to consider the extraarticular disorders associated with generalized joint hypermobility, and there is a very good discussion about the literature that exists out there now, fully well-documented, in the peer-reviewed literature that things like orthostatic tachycardia, functional gastrointestinal disturbances, pelvic and bladder dysfunction, and anxiety are associated with generalized joint hypermobility. They are more common in the population of people with hypermobility than in the general population at large. Any of these may be seen in people with the hypermobility spectrum disorders, and they should be recognized and treated promptly. It's important for us to recognize that any of the comorbidities that we see in any of the Ehlers-Danlos syndromes may also be seen in people with the hypermobility spectrum disorders.

Dr. Levy also talked about why this was not included in the manifestations or in the diagnostic criteria, and we call these associated disorders with the hypermobility spectrum disorder. The committee felt that we do not yet have sufficient evidence to call these extraarticular manifestations true pleiotropic features of generalized joint hypermobility. The recommendation was made that they be considered joint hypermobility-associated comorbidities, and they left open the question as to whether chronic pain is a late consequence of joint hypermobility or a joint hypermobility related comorbidity. The paper states this is still a matter of debate and further research is necessary to clarify this issue.

As you've heard, both from Dr. Kline, Dr. Levy, and many times throughout this weekend, the genetic basis of joint hypermobility, the hypermobility spectrum disorders, and hypermobile EDS remains unknown. I applaud this effort that's being launched through the University of Arizona. This should be a high priority target for future research endeavors. It certainly will help to validate and refine the existing diagnostic criteria, and should guide a more rational approach to management and therapy.

This is the final table from the paper on the framework for considering joint hypermobility and lists the various phenotypes in the hypermobility spectrum, going all the way from asymptomatic joint hypermobility of the different types, to the hypermobile spectrum disorders and hypermobile Ehlers-Danlos syndrome. Finally, the committee offered this kind of visual representation of how to think about the spectrum of joint hypermobility disorders. There's an axis of etiology and another of axis of pathogenesis here. Fundamentally, in this circle, we have asymptomatic joint hypermobility, of which generalized joint hypermobility is a subset. Then, in the presence of pleiotropic manifestations, the other systemic manifestations and organ systems other than the musculoskeletal system — we have the universe of Ehlers-Danlos syndrome, of which hypermobile Ehlers-Danlos syndrome is a subset. Down here we have the soup of hypermobility spectrum disorders, including localized, peripheral, generalized, and historical hypermobility spectrum disorders. Up here, along the pathogenetic spectrum, the joint hypermobility-related comorbidities.

This is indeed a framework for thinking about joint hypermobility. It's a proposal. It's a work in progress. I think it's an enormous contribution to our intellectual rigor in thinking about patients who suffer from these conditions and who experience all that joint hypermobility can throw at them. And, it's recognized that there's still a lot of work for us to do in terms of validating these labels, understanding what they mean, and understanding the genetic underpinnings. I thank you all very much for your attention. Thanks to the authors of this paper — really, I'm presenting their work — and to The Ehlers-Danlos Society and EDS UK, who sponsored the International Consortium, and to Lara Bloom, Shane Robinson, and Sandy Chack for the invitation to be here with you today. Thank you so much.

Q&A

L. Bloom Thank you, to you all. If anyone has any questions if you could just bring them forward and place them on this table, here. We will try to get through them all. So, question number one, "Does puberty trigger a severe presentation of hypermobile EDS symptoms?"

T. Kline So, I also forgot to say that I have no disclosures. I would say that the simple answer to that would be, no.

L. Bloom Thank you. "Stem cell therapy for reducing pain, is it safe and effective?"

C. Francomano That requires a lot of research. We haven't — I don't think we have any published data on the efficacy of stem cell therapy yet, to address chronic pain.

H. Levy I would add to that, that's sort of like asking, "Is there a cure for cancer?" When you give someone stem cells, you are giving them new cells that bring in all sorts of new things — some things good, maybe some things bad. So, I doubt that it's any one treatment, and it would depend very highly on whose stem cells, what they're bringing into the mix, and what's the underlying cause of the chronic pain that it might or might not be helping. My guess is that the evidence will be mixed because it's going to be too heterogeneous.

L. Bloom Thank you. "My adult children do not have the phenotype for EDS, does this mean they do not have the genotype?"

H. Levy No.

L. Bloom Thank you.

H. Levy Alright, I'll elaborate. One of the terms that we teach each other as we're training the next generation of geneticists is "reduced penetrance." A related one is "variable expressivity." Those are words that we still teach each other, but, frankly, I think we should stop using them because most people don't understand them. In English what that means is, you can carry an altered gene that predisposes to disease, but you might not happen to manifest any of the symptoms. Yesterday I talked to you about hereditary breast and ovarian cancer. You can have a mutated BRCA gene and never develop cancer, or you might develop variable expressivity — different manifestations. You might get breast cancer. You might get ovarian cancer. Same thing with almost any genetic change. You might not have any symptoms. You might have variable symptoms.

L. Bloom Thank you. "What should we look for when buying compression garments?" It says here for children, but I imagine it would be the same for both children and adults, so what does one look for?

T. Kline I don't claim to be an expert in compression garments. I think, sometimes, wearing the tights or leggings, or knee socks that have some compression can just help return the blood flow to the heart and to the brain. I don't have any specific recommendations. There may be other professionals out there who could answer that better than I.

C. Francomano I'd like to mention Bauerfeind is one of our sponsors for this meeting, and I've had really good results with the Bauerfeind products. Bauerfeind was a textile manufacturer before they were a durable medical equipment manufacturer, and I've found that their fabrics are very well-tolerated. So that's something to think about, especially for people with sensitive skin, when you're looking at the compression garments you want to get a feel of the fabric and make sure that it's going to be tolerated by people with sensitive skin.

L. Bloom Anyone who has seen "Issues with My Tissues," the documentary I did doing the marathon, I wore SKINS and they worked very well for me as well, so either/or. Bauerfeind are very good. I actually wasn't aware of them when I did it. It was 2011, but both work quite well.

"People have recommended special pillows for neck issues. What criteria should people look for when looking for an orthopedic pillow?"

H. Levy Comfort and efficacy. In fact, for those of you are supporting family members and friends who don't have EDS, the same applies to you. A few years ago, I started waking up in the middle of the night with tingling in my hand, and it was clear to me that I probably have a bulging disc in my neck. I went and got one of those pillows, and now I sleep through the night. It's just good advice, and there's no one-size-fits-all. You've got to figure out what works best for you.

T. Kline I don't know if they're all orthopedic pillows, there's products out there that work with the flow of the body or Tempur-Pedic pillows. There are many products that are available.

C. Francomano Unfortunately, pillows are one of those things that you can't take home and try out and bring back if they don't work, so it's always an investment to try one of them out. It's definitely worth the odyssey to search out the one that's most comfortable because it can make a really big difference to the quality of your sleep and then, therefore, the whole quality of your life.

L. Bloom Okay, "If you're diagnosis moves from hypermobile EDS to HSD, what should your next steps be in regards to a diagnosis and treatment?"

C. Francomano I would say that the next steps are addressing the individual manifestations that are interfering with the quality of your life. If you're having gastrointestinal problems, it's addressing those gastrointestinal problems. If you're having chronic pain, it's addressing the chronic pain. It's exactly the same steps that we would take if you carried a diagnosis of hypermobile Ehlers-Danlos syndrome. The goal is to improve your quality of life, whether your diagnosis is hypermobile Ehlers-Danlos syndrome or hypermobility spectrum disorder.

H. Levy What I've learned in my experience, not just as a geneticist, but a primary care doctor, and I wish I had been taught this in medical school, is that people only ever come to the doctor with one of two questions, "What's wrong with me?" and by corollary, "Do I need to worry about it?" In other words, "What's the diagnosis?" Or, "How do we make this better?" Really the question you have to ask yourself is, "Does the name of the diagnosis matter, and if it does, why does it matter?" What are you looking for? If you can ask your question as precisely as possible, you and we have a better chance of asking it. My hunch is, for most of the people with HSD, the real question, as Clair just said, is how do I feel better. That's where the priority lies. The diagnosis will almost certainly evolve over time, but if you think it matters, try to figure out why it matters. That helps to refine the question, and that then defines your next step.

L. Bloom I have a question here from Professor Rodney Grahame, who has cliché doctor's writing, so I'm struggling to read it. "Is the hypothesis that the different entities will remain constant and different over time, and can one answer this question by purely cross-sectional studies, or will long-term studies be required?"

H. Levy No.

C. Francomano Yes!

L. Bloom There we go!

C. Francomano We never disagree! So, definitely, long-term studies will be required. I'm sure you weren't answering no to that question. Right, Howard?

H. Levy Right.

C. Francomano Okay, I think Howard and I agree that cross-sectional studies are not sufficient and, definitely, we expect that our understanding of these conditions will evolve over time.

L. Bloom "How early do children's symptoms present? If a 2-year-old hasn't presented yet, should we continue monitoring?"

T. Kline So, as we've said, Ehlers-Danlos syndrome is extremely variable. Symptoms can present, potentially, at any age. Symptoms can never present, or the individual could not have symptoms. Typically, joint hypermobility is more common in children anyway. Most of the time we see excessive hypermobility and maybe some symptoms related to that, probably somewhere between the ages of 5 and 10. But, again, there could never symptoms. The other thing is that sometimes there could be an issue when someone's younger, and then they can resolve, and then later on some symptoms could, again, present. I wouldn't over monitor your children. I would just go along and see how the children do, and then if something comes up, in the back of your mind you could say, "Could this be EDS?" Go for an evaluation.

L. Bloom Thank you. "Could yoga and Pilates please be discussed? Is it recommended and should they use full end range?"

H. Levy Yes, highly recommended, but those are just examples. Anything that helps improve muscle tone and stability. Most of you know that I hate the word strength, that's an s-word for me. The distinction is strength is a voluntary force you exert at will. Tone is your resting state of muscle contraction. Yoga and Pilates are great examples, but only examples of things that can help to build tone and stability, and anything that contributes to that is worth pursuing.

C. Francomano I would add, in terms of the range of motion question, often yoga instructors are really enamored in incredible hyperextensibility and they really like to see that, and they encourage people to extend their joints to the full possible range. I think it's probably best to operate within the mid-range when you're doing the yoga, and not really push your joints to the full possible range of motion. Aside from that, I would say yoga is — I would concur with Dr. Levy about the utility.

H. Levy I just wanted to add that going to full range and extending is yet another area that needs a lot more research. There has been one paper that I'm aware of, and I just blanked on her name — physiotherapist from Australia, but 5 years ago published a paper in children with hypermobile joints. She's in Melbourne, Australia?

Sydney, Australia? They took a bunch of kids with hypermobile knees and split them into two groups. They gave them the same exercises. One group they said, just do the exercises. The other group they said, do the exercises but be careful not to hyperextend your knees.

Then they asked both the kids and the parents how they turned out. The kids actually reported either no difference or less pain in the group that wasn't warned about hyperextending. The kids who hyperextended actually were either the same or — I'm sorry, the kids who were warned not to hyperextend may have actually perceived more pain. We don't know why. My personal guess is when you call someone's attention to a joint and they think about it more, then they notice their pain more. The parents, not surprisingly, had a different reaction. The parents thought that if you were hyperextending then you had more pain. Now that I've become a parent I totally get it, that we parents often time see more than might actually be there. So, there's a lack of good evidence, but the one study that I think is pretty good suggests that you may not need to worry about hyperextension, unless, of course, it truly does hurt.

T. Kline I would just add that one of the beauties of yoga and Pilates is the core strengthening, and that's always really helpful for the extremities.

L. Bloom "Is there an ICD-10 code for HSD, or are these people out of luck?"

H. Levy ICD makes us all out of luck.

C. Francomano We have an ICD-10 code for another connective tissue disorder without a specific name. Unfortunately, that's really what we have to use right now. You can use hypermobility of joints, yes.

L. Bloom And that is something the society are taking on as something we want to do, but we have decided that it makes sense to wait until Ghent 2018 because there will be another revision and we don't want to change codes if we then have to do it again. So, we're trying to look at the long game and doing that along with the NICE guidelines in the UK. It is something that's a priority to us as well.

"What would you advise families where women meet the criteria due to the Beighton score and other criteria, but the men in the family don't meet the criteria due to low Beighton, but have all the same joint pain, system issues as their female siblings?"

C. Francomano Treat the symptoms.

H. Levy We struggled with, and during some of the evolution in our criteria, we did have different Beighton thresholds based on sex. But, ultimately, the more closely we looked at it for some sort of evidence to support it, it fell apart and we wound up not including sex-based differences. That was one of the last things to go before the final publication. The one bit of hope I can give you is that the family history criterion – well, it's a different criterion, so I guess it doesn't totally help. More work to be done there, but yes, treat the symptoms. We need a gene.

L. Bloom "Are people with Tenascin-X mutation now classified with an HSD, or still classified within hEDS, or is there a separate category and type?"

H. Levy There's a separate category. We called it classical-like, I think. Do you remember exactly?

C. Francomano So, people who have the autosomal recessive form of Tenascin-X are in a separate category. There are people who have, who are heterozygous, who, in other words, have one copy of the Tenascin-X alteration or variant, who do manifest joint hypermobility. Those people, I think, could fit into the hypermobile EDS if they meet the diagnostic criteria, or HSD otherwise.

L. Bloom "Genetic testing for hypermobile EDS, should I get it? Where to get it? How will it help me?"

H. Levy The writer of the question, I suspect – well, I don't know. If by testing you mean a test of your DNA to find the mutation, I don't recommend getting it now because there is no such test. You'd be spending a lot of money on quackery. If by testing you meant clinical evaluation, seeing a specialist to determine if you do or don't meet the criteria, then, the answer is the same thing that we've been saying several times. If you need that diagnosis for some reason, sure, get it. If you just need to feel better then treat your symptoms.

L. Bloom I'd just like to add to that that, as we've mentioned quite a few times, the society are working on building a global registry at the moment. Alongside with that, working on offering genetic testing. It's very much in the embryonic stages at the moment. As you can imagine, it involves a lot of ethics, cross-border, a lot of things to consider. Within that, we eventually hope to provide people with exome sequencing, which would be in a sense an EDS panel. So, the people that are worried about, do I have another type of EDS? There will be the opportunity to rule that out. Similar to

what the team are doing here, genome sequencing, which is much more of a discovery panel, which we would hope would eventually lead to the mutation.

We've been advised by people that you need around 2,000 people to hope to find some kind of indicator. These things cost in the thousands, so it's very expensive. Like I said, we're still developing the best way to do that. We are aware that there are people that want to have their genes looked into, and we're trying to offer a solution for that. Please be patient with us. It involves a lot. We want to do it right, so that might take a little bit longer. That's a little bit of hope for everyone as well.

"What is the best exercise or sport for children with hypermobile EDS or HSD other than swimming? What about the concern for the development of osteoporosis if only nonimpact sports are done?"

T. Kline Other than swimming, nonimpact sports could include walking, bicycling, some martial arts, the early levels of dance or even gymnastics, but we don't recommend those, generally, because they're too extreme. There's not typically a concern for osteoporosis in the pediatric population.

H. Levy There's lots to unpack in that question. There's still debate as to whether EDS truly does predispose to the disease that we call osteoporosis, or maybe it just makes the bone density test sometimes look a little bit lower. The paradox here is that we don't really see an increase in actual fractures in EDS. We just sometimes see lower bone density. More research could be done there.

My answer to the exercise is, I pretty much never recommend rugby or tackle football. But, other than that, the best exercise is something that the person will do. Because if you hate swimming and you never do it, and you just sit on your butt and eat bonbons, that's not good. But, if it's skiing, if it's running with well-cushioned shoes, if it's running a marathon because that's important to you—whatever it is, if you do it with a minimum impact and just do it because you enjoy doing it, you're going to wind up better than if you did nothing.

T. Kline We also often see teenagers who are involved in a sport, particularly thinking about scholarships for college, and that's an extremely important issue. They just need to be made aware of the risks. I think there's many other contact sports that have some contact, basketball, soccer, there certainly can be blows to the shoulder and pivoting of the hips that can be harmful. As long as the family and the child are aware of all the risks, then, obviously, they should do what they want to do. I agree.

L. Bloom We have a quite a few different questions in different ways about the family and inheritance and things like that, so I'm going to try and piece them together. One question was, and we do get this a lot, "What happens if I'm adopted? What happens if there is no way to trace family history?" Other people have said, "What does family history mean? What am I looking for?" And, "Can it be diagnosed without inheritance? Can you be a new mutation?" If you could develop. I think people are a bit confused about that, and if you could explain that, that would be great.

C. Francomano So, the family history, as Howard mentioned earlier, for the diagnosis of hypermobile Ehlers-Danlos syndrome, it requires a first-degree relative who has independently met the diagnostic criteria, the new diagnostic criteria, for hypermobile Ehlers-Danlos syndrome to say that you have a positive family history for hypermobile Ehlers-Danlos syndrome. A first-degree relative would be your father, your mother, your daughter, your siblings. So, your children, or your siblings, or your parents are basically your first-degree relatives.

If you're an adopted person and there's no possibility of looking at a family member, then, in order to make the diagnosis of hypermobile EDS under the existing criteria, you need to meet the systemic manifestations and the musculoskeletal manifestations. One of the things that is a little unfortunate is that because of that restriction that Dr. Levy mentioned earlier about having an autoimmune condition, if a person is adopted and they have an autoimmune condition, there isn't any way to make the diagnosis under the existing criterion. I think that's an issue that is going to have to be dealt with as we move forward, thinking about this.

H. Levy The plan is, once this research project that was just announced this morning is successful, we're going to rewrite the entire diagnostic criteria, and much more heavily emphasize genetic testing. But, we're just not there yet.

L. Bloom "Prolotherapy, is it helpful?"

H. Levy Sometimes. As I understand, the concept of prolotherapy, it is to inject an irritant to prompt scarring and to count on that scarring to then improve stability of the joint. My sense is that sometimes it helps and sometimes it doesn't. The real problem is that I haven't seen, and maybe I haven't looked hard enough. I haven't seen good studies to truly assess whether it works or not, and for whom it works. What we mostly hear is anecdotal evidence, and people who go to a prolotherapist and do well keep going to the prolotherapist and don't come to someone who doesn't practice prolotherapy. And someone who goes to a prolotherapist and doesn't get better

moves on in search of something else.

People who practice prolotherapy get biased positive reinforcement that it's working because those who didn't benefit left and went elsewhere. And those who don't practice prolotherapy also get biased information, because the patients they see say, "Yeah, the prolotherapy didn't work for me, so that's why I'm here trying something else." That's one of the — it's a good example of inherent biases in research that people often don't realize are there until you step back and think about it. So, yes, it sometimes helps, sometimes not.

L. Bloom This is another question we get a lot, "What if you used to meet the new criteria, but you now no longer do because you've stiffened with age?"

H. Levy Treat your symptoms.

L. Bloom "Loeys-Dietz shares many characteristics in common with hypermobile EDS. What characteristics differentiate the two disorders?"

C. Francomano So, the Loeys-Dietz syndromes have the major differentiating feature is the vascular involvement in those conditions; so, an increased risk of aortic root dilation and tortuosity of the arterial tree, and a predisposition for aneurysms in the arteries in multiple locations. That really is the fundamental distinguishing feature, in my mind. There are some craniofacial features that are also distinguishing and would differentiate Loeys-Dietz from the hypermobile Ehlers-Danlos syndrome.

I've heard Hal Dietz say that if the aorta appears normal on the echocardiogram, it's probably not Loeys-Dietz because they almost universally will express an aortic root dilation at a very early age.

L. Bloom This is a question from Dr. Pocinki. "Why bother including pelvic organ prolapse as a criterion if adult women can't meet the criterion and it's very rare in children and men?"

H. Levy Clair recommends I say "point taken." There's slightly more to it. If you happen to be an adolescent or a man who does have pelvic prolapse, then that is significant and that still does count. I agree with you. It's going to be a rare person who meets that criterion. Do we need to improve those criteria? Absolutely, yes.

L. Bloom Another one from Dr. Pocinki, "Could Dr. Levy please elaborate on the arachnodactyly criterion, which he didn't mention?"

H. Levy That was actually an interesting one in our discussions. So, arachnodactyly literally means "spider-like fingers and toes," a well-known feature of Marfan syndrome and some other related connective tissue disorders. We had some debate and discussion in the group about whether or not to include that in the criteria. In an earlier iteration of the criteria, we actually had another whole different set. We had Marfanoid, or Marfan-like features separate from some of the other connective features. We decided that was getting too rigid and strict and even harder to meet, so we just lumped them all together.

In fact, we softened the arachnodactyly criteria. To meet Marfan syndrome criteria, you have to have both of the two different signs and to meet the EDS version of the criteria you only need one or the other. Those two signs are, can you wrap the thumb and pinky around the opposite wrist and overlap by a full knuckle, and for Marfan syndrome the word would be "and," but in this case the word is "or," can you lay the thumb across the palm, fold the fingers over it without overlapping the fingers, can you make the full nail of the thumb stick out the other side of the hand. If one or the other is positive, we take that as a sign of a Marfanoid-like feature that currently we are looking at as potentially being a diagnostic sign of Ehlers-Danlos syndrome.

But, like everything else, the goal is that the gene or genes would be found, and then we'll do much better studies saying, okay, among people who clearly meet gold-standard criteria, which of these signs and symptoms and features really do associate with EDS, and which ones were just a good guess back in 2017, but turned out to be wrong.

L. Bloom Question, "Is it possible that very specific chronic pain is associated with EDS rather than widespread pain?" So, a very specific point in the spine is what the example is, rather than the chronic widespread pain that we hear about. Would that be more of an injury or something else to consider?

H. Levy What we were going for in the criteria is, if you have localized pain to very one specific spot, that seems not to be so suggestive of a generalized connective tissue disorder like Ehlers-Danlos. So, we encourage looking hard for what's going on right there to cause that pain. I'm intentionally not saying absolutely, no. But, playing the odds, highly localized pain seems much less likely suggestive of Ehlers-Danlos syndrome than pain throughout multiple limbs, or generalized widespread pain.

L. Bloom We've had quite a few people asking about the Cusack protocol. Could you comment on that at all?

C. Francomano I think her first name is Deborah, Cusack – has developed a nutritional protocol designed to address both the musculoskeletal and some of the gastrointestinal issues that many people experience with hypermobile Ehlers-Danlos syndrome. This protocol includes the use of a number of vitamins, other nutrients. She used aloe juice very heavily and it's been very effective for her and for her family. It's another one of these things that we really don't have any peer-reviewed, scientific evidence to support. It seems to me that there's very little downside in trying it. So, for people who are interested, I think it's something that's worth looking into. But, we don't really have any evidence to say one way or the other how effective it is.

L. Bloom Thank you. "Can you address the question of the comorbidities of ADHD and autism spectrum? Is it associated with EDS?"

T. Kline So, as I said, we have a certain percentage of the children that we've seen with EDS who have autism spectrum disorder and/or ADHD. I can't really address this. I suspect it's more the general population risk rather than being related Ehlers-Danlos syndrome in general.

L. Bloom "Because of the chronic widespread pain, should time-release opioids be used?"

H. Levy I've evolved my thinking very much in the last 15–20 years; 15–20 years ago I had to convince people in chronic pain to take opioids, and I now deeply regret that. My answer to that question is, opioids should be avoided if at all possible. If you're going to use opioids, I recommend using the least amount possible. For those who are going to use opioids, my understanding of the literature is that there's probably less risk of dependency and tolerance if you use time-release opioids. On the other hand, the more opioid you're exposed to, and the longer you're exposed to it, the greater risk of serious long-term complications, including actually making the pain worse. So, it's a high-risk proposition to start taking opioids and you really should be in the hands of an expert in use of opioids if you're going to go that route. That's my current thinking. I reserve my right to change my opinion 10 more years from now.

L. Bloom A couple of questions about progression, so I'll merge them. "Is EDS a progressive disorder? Does it intensify with subsequent generations?"

H. Levy Marco Castori addressed this, and it was in my slide set but I spoke too long and didn't get to it. I'm going to cheat and jump to it now. This is in the summary paper about the natural history of EDS. So, the framework that Marco has laid out, which a lot of really liked and think makes good sense, is this: that there may be three phases thought about in Ehlers-Danlos syndrome in terms of progressions. Earlier in life, more of a hypermobility laxity phase, maybe a little fatigue but not as much pain. And then a second phase with much more pain and fatigue, sometimes getting labeled with fibromyalgia and then starting to develop some of these other systemic involvements. And then beyond another milestone that's a moving target, moving more into stiffness, reduced mobility and primarily featuring pain and fatigue.

The critical thing here is that this is a very generalized trend. There is no specific landmark at which one might move from one stage or phase to another, and not everybody goes through all stages. So, yes, it can progress, at least in this way, but does not always progress. While we lack good evidence, I think many of us believe that following the advice that we've been preaching — stabilizing exercises, remaining active, avoiding impacts, all those protective things, using the braces and the compression garments — the hope is that we can slow or perhaps halt some of that progression to these more severe stages.

L. Bloom "Are autoimmune disorders more common in EDS, and if so, why?"

C. Francomano This is another one of those questions for which we don't really have very good scientific evidence, but my clinical impression is that it probably is more common, that autoimmune conditions are more common in patients with the hereditary disorders of connective tissue. There are several theories as to why this might be. We don't really know for sure. My clinical impression is that there are more patients with the various autoimmune conditions in the population of patients that I see than I would expect in the general population. What do you think, Howard?

H. Levy I think the opposite. I suspect — this is why we need research, right? Because what I think and what Clair thinks, and what any of you think, doesn't really matter. The fact is what the fact is, but the fact is that we don't [know] the fact yet. My belief is that we may have mislabeled some folks with autoimmune connective disease as having a heritable connective tissue disease. Ultimately, we just need better research to figure it out. What they all share in common is connective tissue disease. What we're quibbling over is, is it heritable, genetic, born with an error in the way your body makes its connective tissue, versus acquired. Did your immune system or some other attack or insult to your body start to degrade the otherwise normal connective tissue?

At the end of the day, they're all connective tissue diseases. They have different underlying etiologies and causes and may have different implications, complications, and treatment approaches. It is important to answer these questions, but I don't think we have a good answer today.

L. Bloom Okay, I'm going to merge three similar questions. "Is there any impact on birth control choices? Estrogen versus progesterone? Do menstrual cycles make the pain and symptoms worse? Does menopause affect symptoms?"

H. Levy That's hypermobile EDS and pregnancy. "Yes" to increased laxity during pregnancy. "Yes" to rapid labor, which is good if it's 4 hours instead of 20 hours, maybe not so good if it's 30 minutes instead of 4 hours. Again, Marco published an interesting paper looking at systemic manifestations – pain, GI, *et cetera* – and found that some people actually got better, many people stayed the same, and some people got worse. All the rest of the stuff that you hear and read about impact on fertility, about preterm birth and miscarriage, about increased bleeding, and about whether you must have vaginal birth or must have Cesarean birth – I want to say it's hogwash, but the more politically correct way to say it is, there's no evidence to support any of those claims. Talking about hypermobile EDS, different for the other types of EDS.

L. Bloom "Birth control and menstrual cycle, and does menopause make it worse?"

H. Levy Hormone replacement – taking estrogen and progesterone, whether as a birth control or postmenopausal – in my anecdotal experience, does impact many of the symptoms that folks with EDS develop. But I don't think there's a one-size-fits-all answer to that. I think that's highly individualized. At menopause, lots of things change. Lots of things change positively or negatively, yes.

L. Bloom No, the birth control question. You said they impact the birth control. Do they impact positively or negatively?

H. Levy Oh, just birth control? Maybe I didn't fully understand the question.

L. Bloom "Birth control: does it impact negatively or positively, and should there be one better estrogen over progesterone over the two?"

H. Levy I think whether or not to use it and which one to use is not clearly understood and is probably different from one person to another.

L. Bloom When you said it impacted patients, do you mean negatively or positively?

H. Levy The impact of hormones can be either direction. Many women find that regulating their menstrual cycle reduces their migraines, so that's certainly a positive. Some people report that taking estrogen or progesterone might increase their laxity or decrease their laxity. It might increase or decrease their pain. I've seen everything all over the map. I don't think there is a single answer to that.

C. Francomano There are many young women, when they start menstruating, start experiencing a lot of pelvic pain and pain with menstruation, and excessive bleeding with menstruation. These can be quite disabling symptoms. So, sometimes, the use of hormone replacement or birth control pills to alleviate those symptoms can be really life-changing. It can make a very, very positive impact. I wouldn't ever say to somebody, don't try them because of fear of exaggerating the joint laxity or whatever concerns people might have because they really can be extremely helpful.

I have heard from people that there are certain — some people do well with one preparation, other people do better with others. It probably has something to do with the way we metabolize various drugs and the genes involved in that. It can be kind of a trial and error to get to the best possible preparation for that indication.

T. Kline I would just add, generally starting with the lowest doses is what people recommend, and then going up if needed.

L. Bloom Two questions here that I'm going to answer, if that's okay, panel? The first one is, "I heard that England has found a cure for EDS." No one told me! "America is far behind. Is that possible?" No. Definitely, there is no cure for EDS in the UK or the USA or anywhere. Yes, in some areas, the UK is a little bit more advanced. For example, in the GI area, we have an incredible Professor Aziz over there and Adam Farmer, who's flown over here to talk to you today. And, in that area, yes, we are a little bit more advanced, but there are a lot of areas that the US is advanced. For example, Chiari and neck instability, and something that at the moment in the UK you can't even get an upright MRI.

So, it swings in roundabouts. We've also, as we've started the society we've been reaching out all over the world to various different countries, and we realized just actually how lucky we are in the kind of progressed western world. When we were in India in January with our conference there were a small handful of geneticists for the millions of patients that are out there needing it. It's tough, but we have got it good.

The last question is, "What is the best literature website we can direct doctors to that do not understand EDS?" The Ehlers-Danlos Society website, of course! We have – it's developing all the time, but we do have amazing resources on there. We're also, in the next couple of months, going to have lay versions of all the papers on there, so you can read them, digest them, give them to friends, give them to colleagues. We also have all 18 on there for your doctors. We are doing webinars just for doctors in the future as well. We have papers on there. Every single paper that was peer reviewed as part of the symposium, we are uploading onto our medical article sections, so you can point your doctors in the direction if they ever wanted to read any paper about EDS or comorbidities, they will find it on our website.

We are going to have resources and useful links on there, so that not only you can find us, but you can find other EDS charities around the world, support groups, and everything you would ever need to know about EDS is on our website. Please do visit us. Thank you very much! Thank you to our amazing panel. Sorry, we didn't get to everyone's questions, but you will be around for the rest of the day if anyone wants to ask some specifics.

Transcription by Christina Cole