

Dr. Clair Francomano and Lara Bloom

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<https://youtu.be/3iw4uJeAKj8>

C. Francomano This is Clair Francomano and Lara Bloom and we are here to talk about the 2017 International EDS Classification. This is really a landmark day in the history of the Ehlers-Danlos syndromes. The *American Journal of Medical Genetics* is publishing 18 articles today that summarize the current state of knowledge about the Ehlers-Danlos syndromes and related disorders, and it is really a great pleasure and a privilege today, to be able to represent the international consortium to discuss the information that has been presented in these 18 articles in the *American Journal*.

L. Bloom Welcome, everybody.

C. Francomano The classification of the Ehlers-Danlos syndromes has not really been addressed since 1997 when the Villefranche nosology was put forward. This was published in a paper by Beighton et al in *The American Journal of Medical Genetics* in 1998. At that time, there were six major types. You can see them listed on the slide. They included the classical type, the hypermobility type, the vascular type, kyphoscoliosis, arthrochaliasia, and dermatosparaxis types. Even back in 1998, the molecular cause for five of these disorders was known, but the hypermobility type was not, then, and is still not known. It was really more than time for a revision of the Ehlers-Danlos syndromes classification.

This whole process began in Ghent in 2012. There was an international meeting sponsored by Dr. Fransiska Malfait and Dr. Anne De Paepe in 2012 in Ghent. There was another meeting in Paris in 2013 and in Glasgow in 2015. The process really got a huge boost when the Ehlers-Danlos National Foundation, which was the charity name at that time, and EDS UK came onboard and committed substantial resources to putting forward an international symposium in New York in May of 2016.

The work that I am going to present to you today is the outcome of that enormous effort that went into developing the symposium in New York, and then the subsequent effort to develop these papers that are being published in *The American Journal of Medical Genetics*. We anticipate that there will be another meeting in Ghent in 2018, at which time we will be able to review what has happened since the implementation of these new diagnostic criteria and the new classification, and certainly we expect that this will be under revision at that time.

The goal of the Ehlers-Danlos Syndrome Symposium in May, in New York—there were three. We were to build a revised nosology or classification, that defines the diagnostic criteria, define new Ehlers-Danlos syndrome types where necessary, and to begin the process by which management and care guidelines are being developed for each Ehlers-Danlos syndrome subtype. There were several committees and working groups that were set up to spearhead this process. The steering committee consisted of the chairs of the four committee types.

There was a classical committee, which I had the privilege to chair. Brad Tinkle chaired the hypermobility committee. Peter Byers shared the vascular committee and Fransiska Malfait chaired the committee

that considered all of the rarer types of Ehlers-Danlos syndrome. Then there were a number of working groups looking at a wide range of different issues related to the Ehlers-Danlos syndromes. They are listed here on this slide. The working groups were designed to look at issues related to comorbidities and different organ system involvement in the various types of Ehlers-Danlos syndrome.

As a result of these deliberations, there is a new classification of the Ehlers-Danlos syndrome types. The list is on this slide at this time. It starts with the classical type of Ehlers-Danlos syndrome, and then the classical-like Ehlers-Danlos syndrome, which is autosomal recessive. The three major types which I am going to discuss today are the classical type, the vascular type, and the hypermobile type of Ehlers-Danlos syndrome.

We will start with the classical type of Ehlers-Danlos syndrome, which we will abbreviate cEDS. The major criteria for this condition are skin hyperextensibility and atrophic scarring, and it should be pointed out that the skin extensibility in the classical type of EDS is extreme. The joint hypermobility is the second major criteria. The minor diagnostic criteria include easy bruising, soft doughy skin, skin fragility, which may result in traumatic splitting, molluscoid pseudotumors, subcutaneous spheroids, hernia or history thereof, epicanthal folds, the complications of joint hypermobility, and a family history of a first-degree relative who meets the clinical criteria.

The committee's recommendation for establishing a clinical diagnosis of classical Ehlers-Danlos syndrome is that a person should have major criteria, which is the skin hyperextensibility and atrophic scarring, plus either the joint hypermobility or three of the eight major criteria. The committee felt strongly that confirmatory analysis is recommended for any patient meeting the recommended clinical criteria. Molecular analysis of the *COL5A1* and *COL5A2* genes identifies a causal mutation in more than 90% of the patients, and this should be used as the standard confirmatory test. In some situations, genetic testing may not be available, and in that situation, electron microscopy findings of collagen flowers on skin biopsy can support the clinical diagnosis. The absence of these confirmatory findings does not exclude the diagnosis, but alternative diagnoses should be considered in the absence of type V collagen gene mutation or electron microscopy findings.

Moving on to the vascular type of Ehlers-Danlos syndrome, the major criteria include a family history of vascular Ehlers-Danlos Syndrome with a documented causative variant in *COL3A1*, arterial rupture at a young age, spontaneous sigmoid colon perforation of the absence of known diverticular disease or other bowel pathology, uterine rupture during the third trimester in the absence of a previous C-section, and/or severe peripartum perineum tears, and the presence of a carotid cavernous fistula in the absence of trauma. There are numerous minor criteria. I will just read through them briefly. These include bruising unrelated to identified trauma, thin translucent skin with increased venous visibility, characteristic facial appearance, spontaneous pneumothorax, acrogeria (an aged appearance at an unusually young age), talipes equinovarus (clubbed feet), congenital hip dislocation, hypermobility of the small joints, ruptures of the tendon or muscle, keratoconus, gingival recession and gingival fragility, and early onset varicose veins.

The committee for vascular Ehlers-Danlos syndrome suggested the following minimal criteria: the family history of the disorder, the arterial rupture or dissection in individuals under 40 years of age, unexplained sigmoid colon rupture, and spontaneous pneumothorax. It was felt that in the presence of

other features consistent with vascular EDS, all of these or any of them should lead to diagnostic studies to determine if the individual had vascular Ehlers-Danlos syndrome. Testing for vascular EDS should also be considered in the presence of a combination of the other minor clinical features listed on the previous slide. The diagnosis of vascular EDS rests on the identification of a causative variance in one allele or one copy of the *COL3A1* gene.

Moving on to the hypermobile type of EDS, which we are abbreviating hEDS. These new criteria were designed to emphasize the syndromic nature of this condition to reduce clinical heterogeneity and to facilitate research into the underlying cause or causes of the condition. It is certainly expected that further clinical experience and research will lead to a revision of these criteria with time. The 1997 criteria for the hypermobility type of EDS, which is what it was called by the Villefranche committee, were there were major criteria including skin involvement with hyperextensibility and/or smooth velvety skin, and generalized joint hypermobility. The minor criteria listed at that time included recurring joint dislocations, chronic joint or limb pain, and positive family history. The Beighton publication in 1998 did not give very explicit recommendations as to how these major and minor criteria were to be applied in the diagnosis of the hypermobility type.

The presence of one or both of the major criteria was considered to be necessary for a clinical diagnosis, but when you look at it that meant that a person with skin involvement only, which could just be smooth velvety skin or hyperextensible skin, could be diagnosed with the hypermobility type of Ehlers-Danlos syndrome. It was strongly felt that a new set of criteria were necessary to homogenize the clinical diagnosis for this condition. The committee really spent an enormous amount of time thinking about this and weighing different solutions, and what they have come up with is that the clinical diagnosis of hypermobile EDS requires the presence of three new criteria. We are calling these criteria 1, 2, and 3.

Criterion 1 is generalized joint hypermobility, abbreviated GJH. The main tool that we use to assess for generalized joint hypermobility is the Beighton score, which is the same Beighton score we have always been using. It is a nine-point scaled to assess hypermobility. New cutoffs have now been recommended for the definition of generalized joint hypermobility using the Beighton scale; for prepubertal children and adolescents a score of greater than or equal to 6, for men and women post-puberty and up to age 50 a score of greater than or equal to 5, and for men and women older than age 50 a score of greater than or equal to 4. The committee also felt that if the Beighton score is one point below the cutoff and the five-point questionnaire regarding joint hypermobility, which I will describe to you in a minute, if that is positive with at least two positive items, a diagnosis of joint hypermobility may be made.

The five-point questionnaire asks the following questions: can you now, or could you ever, place your hands flat on the floor without bending your knees? Can you now, or could you ever bend your thumb to touch your forearm? As a child, did you amuse your friends by contorting your body into strange shapes, or could you do the splits? As a child or teenager, did your shoulder or kneecap dislocate on more than one occasion? And finally, do you consider yourself to be “double jointed”? So just to reiterate, if a person has two positive answers, two affirmative answers, to the five-point questionnaire, and their Beighton score is one point below the cutoff we can establish a diagnosis of generalized joint hypermobility.

Criterion 2, we need two or more of the following features—stay with me now, this is going to get a little

complicated. We have A and B, B and C, or A and C to meet criterion II. The features are: A is systemic manifestations of a more generalized connective tissue disorder, B is a positive family history, and C is musculoskeletal complications. I am going to describe in detail what the requirements are to meet each of those features.

For feature A, at least five of the following features must be present, and these are continued on the next slide. There are two slides with systemic manifestations, they include unusually soft or velvety skin, mild skin hyperextensibility, unexplained stretch marks without a history of significant weight change, bilateral piezogenic papules of the heel (those are those little bumps that pop up when you stand on your heels), recurrent or multiple abdominal hernias, atrophic scarring involving at least two sites without the formation of the typical scars that we see in the classical type of Ehlers-Danlos syndrome, pelvic floor, rectal, and/or uterine prolapse in children, men, or women who have never had children without a history of morbid obesity and or other known predisposing medical condition, dental crowding with a high or narrow palate, arachnodactyly (long, thin fingers) as defined by one or more of the following: a positive wrist sign and a positive thumb sign, the arm span to height ratio greater than 1.05, mitral valve prolapse, mild or greater based on strict echocardiographic criteria, and finally an aortic root dilatation with a z-score greater than +2. To meet feature A, which is systemic manifestation of a more generalized connective tissue disorder, we need five or more of this list of systemic features.

Feature B is relatively easy. This we can get easily—positive family history, one or more first-degree relatives independently meeting the diagnostic criteria for hypermobile EDS. Feature C is the musculoskeletal complications, one of the following: either musculoskeletal pain in two or more limbs recurring daily for at least three months, chronic widespread pain for more or equal to three months, and recurrent joint dislocations or frank joint instability in the absence of trauma. This may either be three or more atraumatic dislocations in the same joint, or two or more atraumatic dislocations in two different joints occurring at different times, or medical confirmation of joint instability at two or more sites unrelated to trauma. If you have one of these three issues, that would meet these criteria for musculoskeletal complications and thereby meeting feature C.

For criterion 3, all of these needs to be met. These are basically exclusionary criteria. We need the absence of unusual skin fragility, which should prompt consideration of other types of Ehlers-Danlos syndrome. Unusual skin fragility will typically not be a feature of the hypermobile type of Ehlers-Danlos syndrome. Next, it is very important that we exclude other heritable and acquired connective tissue disorders, including autoimmune rheumatologic conditions.

Now, we know that people who have the hypermobile type of Ehlers-Danlos syndrome may also have some of the autoimmune rheumatologic conditions, but in patients with an acquired or autoimmune connective tissue disorder, the additional diagnosis of hypermobile EDS requires meeting both features A and B of criterion 2. We cannot use the chronic pain feature because that may be related to the autoimmune or acquired connective tissue disorder. To establish the diagnosis of hypermobile Ehlers-Danlos syndrome in the presence of an acquired or autoimmune connective tissue disorder, we need both features A and B for criterion 2.

Finally, we want to be sure that we exclude any alternative diagnoses that may also include joint hypermobility by causing hypotonia or muscle weakness and/or connective tissue laxity. Basically, we just want to be sure that we have excluded all other possible diagnoses in establishing the diagnosis of hypermobile Ehlers-Danlos syndrome.

When we think about a syndrome, the definition is a pattern of anomalies, at least one of which is morphologic and known or thought to be causally related. The presence of joint hypermobility in combination with secondary musculoskeletal anomalies alone does not really suffice for delineation of a genetic syndrome. Joint hypermobility may occur independently or in the context of multiple different genetic disorders. If you look at OMIM for joint hypermobility, I think there were over 160 genetic diagnoses that come up with joint hypermobility.

It is really very important for us to establish a classification for joint hypermobility. Dr. Castori and his colleagues, and Dr. Tinkle and his colleagues have really—they have labored very, very hard to think about a way in which we can have a framework for thinking about joint hypermobility and the hypermobile type of Ehlers-Danlos syndrome. Dr. Castori and his colleagues have laid out this idea of thinking about joint hypermobility along a spectrum.

When we think about it, we can think about people who have asymptomatic joint hypermobility. There are people who have very lax joint, but it does not bother them at all. They go about their business. They may be able to do some tricks. They may never even come to attention, and that joint hypermobility may be localized just in one or a few joint, it may be generalized meeting the Beighton criteria for joint hypermobility, generalized joint hypermobility, or it may be limited to the peripheral joints, which are the small joints of the fingers/toes and hands/feet. That is one classification of people with joint hypermobility who do not suffer from any symptoms related to that joint hypermobility.

Then there are people with well-defined syndromes with joint hypermobility, and this will include the various types of Ehlers-Danlos syndrome, and it will also include many other genetic disorders, which need to be considered when a person presents to the physician, the diagnosing physician, for evaluation of joint hypermobility. Finally, there are going to be many individuals who have symptomatic joint hypermobility, but who do not meet the diagnostic criteria for a specific syndrome. To include those people in our diagnostic classification, we have now put forward the idea of the hypermobility spectrum disorders.

This table summarizes the spectrum of joint hypermobility and the relationship to the Beighton score and musculoskeletal involvement. We may have asymptomatic generalized joint hypermobility, in which the Beighton score will be positive for the person's age, but the musculoskeletal involvement will be absent. In asymptomatic peripheral joint hypermobility, the Beighton score will usually be negative, because the peripheral joint hypermobility is limited to the hands and feet. In asymptomatic localized joint hypermobility, the Beighton score will also be negative because the joint hypermobility is limited to one or just a few joints.

In generalized hypermobility spectrum disorder, the Beighton score is positive and musculoskeletal involvement is positive. These are people who are symptomatic. They may experience pain. They may experience dislocations, subluxations. They may have many of the comorbidities that we now associate with the hypermobile type of Ehlers-Danlos syndrome, but they may not meet the diagnostic criteria

for hypermobile EDS; and therefore, we will call them “generalized hypermobility spectrum disorder.” Peripheral hypermobility spectrum disorder is people who are symptomatic. The Beighton score may be negative, but the musculoskeletal involvement is positive. The joint hypermobility in these people will be limited to hands or feet, but they may be suffering from pain, from subluxations, from dislocations, from all of the things which may impact quality of life. So we now have a label, a name to provide to these people. This is peripheral hypermobility spectrum disorder.

Similarly, for the localized hypermobility syndrome disorder, because the joint hypermobility is limited to single joints or body parts, or just a few joints or body parts, the Beighton score will be negative, but that musculoskeletal involvement is there. These are symptomatic people. So, we call them the localized hypermobility spectrum disorder. The important thing to remember is that we must address the symptoms as they are presented and the management of those symptoms is our major goal. H-HSD is the term that we are using for the historical presence of hypermobility. The person may not be hypermobile now but may have been hypermobile in the past. In these people the Beighton score may be negative now on exam, might have been positive previously, but still they are experiencing the musculoskeletal involvement that impacts the quality of life, and so they fit into this hypermobility spectrum disorder.

In hypermobile Ehlers-Danlos syndrome, the Beighton score is positive. Musculoskeletal involvement may or may not be present according to the diagnostic criteria I presented earlier. We have now a spectrum of joint hypermobility that ranges from asymptomatic through symptomatic, all the way to the hypermobile type of Ehlers-Danlos syndrome. Now, two questions that have come up a lot since these diagnostic criteria have been known and discussed, [one] is, “Why were comorbidities not included in the hypermobile EDS diagnostic criteria?” This is one question that has come up quite a bit. I would say that we really do not know enough yet about the relationship and causation between the various comorbidities and hypermobile Ehlers-Danlos syndrome, or any of the other types. So we really hope that further research will enable us to establish these causative relationships between the comorbidities and the many different types of Ehlers-Danlos syndrome.

Another thing that people have been very concerned about is, they say, “I do not know if I meet all those diagnostic criteria. Will my diagnosis be changed?” I would say to that unless you have a reason to seek a change in diagnosis, there is no reason to do that at this time. If you are interested in seeing whether you meet the more stringent criteria for hypermobile EDS, you may certainly speak with the physician who made your diagnosis to see whether you meet the new criteria. To me, the most important thing to remember is that treatment and management are paramount. Whatever symptoms you are experiencing should be addressed regardless of your diagnosis.

Thank you all for your attention. I am going to turn the webinar over to Lara Bloom, who is going to be discussing the role of The Ehlers-Danlos Society moving forward.

L. Bloom Thank you so much to Clair for going through the new classifications with us. I am now going to talk to you about what we will do as your charity going forward. I would like us to remember all this work has been done. Apart from the incredible individuals and hubs of expertise dotted around the world, EDS has been one of the most neglected disorders in modern medicine. As patients, we are not

listened to, respected, validated, managed, diagnosed effectively, or given a give chance to live an improved quality of life. We were trying to fix something that was broken, and with these new official criteria that now replace the Villefranche criteria, we can do that.

So what will The EDS Society to spread this new classification? We plan to start on updating the ICD-10 codes that insurance companies use. Currently, there is only one for all the types of EDS. It needed to be updated anyway to reflect the different types, and now we need to introduce the [audio interruption]. Until then, [audio interruption] diagnosis will mean that won't get covered by your insurance. Clinicians are able to use symptom-specific codes to get you treated, and many use this currently anyway. We do not foresee that these changes will make it harder to get anything covered, quite the opposite. These changes will now enable us to put these right.

We will send our plan to work with the WHO, which is the World Health Organization, to get these guidelines internationally accepted. By forming our international consortium and having collaborative research and agreement, we are now much closer to this being a reality. The society is also proud to announce that we are now an associate member of Rare Diseases International, and I plan to go to their next conference in Barcelona in June. We hope that this relationship will help us further in spreading awareness. Now that we have a newly revised nosology, we can also continue our efforts to get NICE guidelines. For those outside of the UK, this is the National Institute for Health and Care Excellence, guidelines in the UK. These are used when anybody is following a diagnostic pathway. These are essential to improve the NHS treatment for those suffering in the UK and it really is high on our list of priorities.

I am pleased to say that there is progress being made. When I have more information that I can share, we will do with all of you. The society and consortium members will also continue to attend conferences to educate and talk about the new criteria. Dr. Alan Hakim, a member our medical and scientific board and the consortium, has organized a session at the upcoming British Society of Rheumatologists conference to discuss the work. I am excited for the opportunity to help present this to that audience. The society will also continue to talk at events with other umbrella organizations such as Dysautonomia International, EURORDIS, Rare Diseases International, and Rare Diseases UK, and so on. We also aim to expand our opportunities to encourage student exchange amongst the clinics and specialists that we have on the consortium so that we can educate the medical professionals of the future.

A question that has come up a lot is, "Will the society now support those with HSDs?" The answer is, absolutely! We will support all those with the Ehlers-Danlos syndromes and related disorders such as HSD, mast cell, POTS, and so on. This publication will not change that. You will all still be in our focus when we are planning research, events, and conferences.

How can you help? Firstly, it starts with us. You need to be the change that you want to see in the world. You need to use the correct terminology. We provided a table on our "Frequently Asked Questions" and we are really asking that people use the right terminology. They are very small changes, but the implications of using the wrong ones will not help us achieve consistency globally. It used to be Ehlers-Danlos Syndrome. We are now leading to recognize all the different types, and it is the Ehlers-Danlos syndromes. It was hypermobility EDS. It is now hypermobile EDS. It was HEDS, VEDS, CEDS, etc. It is

now hEDS, vEDS, cEDS. It was joint hypermobility syndrome or benign hypermobility syndrome or hypermobility syndrome.

These are no longer going to be used, and this is now going to be the new criteria for the hypermobility spectrum disorders. The most important one, that even some clinicians are still using, even though they were stopped in 1997, people are using type III, type IV, etc. Please do not use these descriptors. Use the wordings and the names and the abbreviations as we mentioned. This will really help us, as we mentioned. This will really help us to achieve that consistency.

I would like everyone to keep in mind this: together we can dazzle. In the weeks, months, and days that follow this new classification, because I was very disappointed by the social media reaction when we first posted our FAQs; unfortunately, due to the information being leaked, we were forced to put something out there earlier than we had planned to. It was not the process or the order of things that we would have liked, but we had to respond to the fear and the questions that were arising. Let's remember we are a small community. The charity has many people just like you working for it, and this effort was made possible by clinicians and patient experts to help improve our lives. I ask for you all to please go forward with positivity and support for each other, and help us as your charity vested in everyone's best interest.

What else can you do? You can print out the papers. Take them to your doctors and share them as far and wide as you can. This was not done for the society. This was done for every national charity and organization, and this was done for every single patient and family living wherever you are in the world. The entire supplement will be free to download via our site for three months, and the classification paper will be free to download long-term. After the three-month period, the papers will individually be available on our website for free. There will never be a time that you cannot access this information with no charge. In the next few weeks, we will also be uploading lay versions of all the papers for you to read if you find the original material too complicated. We are also currently looking for ways to have it translated.

Another question that keeps coming up: is it rare [audio interruption]? As you know, the zebra is associated with our community. The reason for this is because medical students have been taught for decades, when you hear hoof beats behind you, don't expect to see a zebra. In other words, look for the more common and usual, not the surprising diagnosis. But many of us spend years pursuing a diagnosis for disorders that are not well known or are not expected in someone who looks normal, or too young or old to have so many problems, or even too rare for anybody to be diagnosed with it. The zebra has become our symbol. Sometimes when you hear hoof beats it really is a zebra. Ehlers-Danlos syndromes are unexpected because they are rare and the hypermobile spectrum disorders are common but unexpected because they remain misdiagnosed or underdiagnosed.

When you see a zebra, you know it is a zebra, but no two zebras have identical stripes, just as no two people with Ehlers-Danlos syndromes or HSD are identical. We have different symptoms, different types, different experiences, and we are all working towards a time when medical professionals immediately recognize someone with EDS or HSD. As everyone knows, my favorite part of being zebra is that a group of zebras is called a dazzle. We are a community of individual zebras. We are stronger together and we dazzle.

In reality, our community probably looks a little more like this: all of the EDS types currently fall under

the rare category, but we know that those living with HSDs are much more common. We cannot really state true prevalence in either group because we need to do more epidemiology studies, and finally prove how common and how rare these disorders really are.

Another question that has come up is will you be changing the name of the charity? The answer is no. We only just launched in May and we really feel that our branding, messaging, and mission reflect our supports and focus on EDS and all the related disorders that now include the hypermobility spectrum disorders. We have updated our website with this in mind. Some of the changes will be on there today and some of them will take the next few weeks to come through, so please be patient with us. We hope that we have addressed some of your concerns.

We now are going to switch over and start answering some of your questions.

Is this publication official? Does it replace the old publications like that of Villefranche or Berlin, and is this what the doctors will be using to diagnose EDS?

L. Bloom I think the answer to that is yes. This is official. This is internationally agreed upon and this will be [audio interruption] Villefranche, the Brighton criteria, and Berlin. So, yes. This is official.

In selective countries and states around the world, EDS is considered a bleeding disorder. Is it known if most bleeding disorder patients have EDS or a family history of EDS?

C. Francomano There is a subset of patients with Ehlers-Danlos syndromes, one of the types of Ehlers-Danlos syndromes, who have bleeding disorders. The exact nature of that bleeding disorder has not really been very well characterized, but certainly, if people have joint hypermobility and a tendency for bleeding, evaluation by a hematologic expert would be warranted for sure.

How can tethered cord be diagnosed in hypermobile EDS patients?

C. Francomano There are a number of questions that we use to ascertain whether a person is likely to have a tethered cord. This is a little out of the scope of our intent for this webinar at this time, but I would say that I would like to refer you to the neurology paper in the journal, which will be available today. There is quite an extensive discussion on that subject.

What is the recommendation for hypermobile EDS in terms of how often they should see cardiologists if there are no known heart issues? Are there any now agreed standards of what they should do in terms of regularly seeking out care?

C. Francomano In terms of the cardiology, if a person has had an echocardiogram as an adult, and that echocardiogram has been normal, there have been several publications now suggesting that follow-up can be pushed forward to every 5 years. In fact, one publication suggests that no further echocardiogram evaluation is necessary. I would make that decision in conjunction with your cardiologist. Certainly, the annual echocardiograms that we used to do, we have a pretty good sense that those are no longer necessary.

Will the new classification help find the hypermobile gene?

C. Francomano I think there is a good chance that it will because if we take a group of people who meet these much more stringent diagnostic criteria for hypermobile Ehlers-Danlos syndromes, we will have a much more homogenous group of people with which to look for the gene. I think that one of the problems we have had so far is that we have had a very heterogeneous group of people because they ranged all the way from the asymptomatic generalized joint hypermobility to the most severely affected and symptomatic people. They were not very rigidly defined on a clinical basis. It may be that that's one of the things that is contributing to the challenge that we have had in identifying the molecular cause or causes.

L. Bloom I would also like to add at this point, as we have mentioned previously, The Ehlers-Danlos Society are working very hard with the consortium to build an international registry. We believe that we are making this incredibly detailed and looking at lots of different aspects, covering all the different forms. We really believe that this registry will lead us to finding the gene or at least give us pathways to doing that. That is the most important thing that we are now doing. Now that we have the knowledge and the criteria from this work, we can now go about building this registry and really learning much more about this, proving how many people are living with it, and the thing that we are lacking completely is evidence. That is what this registry will help provide us with.

There have been different definitions of dislocation versus subluxations. Could you please define a dislocation?

C. Francomano I am a geneticist, not an orthopedist, but I would say my understanding of a dislocation is when the joint is completely separated, for example, if the shoulder is completely out of joint. It is a subluxation if it is only partially out of joint. Dislocations are typically much more difficult to replace and the subluxations, more often, people will be able to manipulate them back into location. There may be a more precise definition from my orthopedic colleagues, and I will look forward to getting that to you if we hear from them about that.

Will other doctors, apart from rheumatologists and geneticists, be able to make a diagnosis hypermobile EDS or HSDs based on the new criteria?

L. Bloom I will answer that by saying yes, and Clair can add anything. The reason we have done this is because we want to make it much, much easier across all disciplines for someone to walk into their office and for them to be able to use these criteria and diagnose it effectively and reliably. There were too many geneticists in the US and too many rheumatologists and geneticists in the UK and Europe being heavily—lots and lots of waiting lists from people that could only seek a diagnosis from these people. Going forward, we want to relieve that pressure and make this much, much easier for anyone to get a diagnosis (a.) no matter where you live in the world, and (b.) no matter what specialist you go and see.

C. Francomano As I was thinking about this last night, I was thinking we really should develop a checklist that is a simple piece of paper that people can bring to their physicians so we can go through the criteria very easily and check off yes/no, and then do the calculation. Eventually, we may actually even be able to develop an app that enables us to do that.

L. Bloom Again, going back, I do not think people realize the enormous impacts that this publication is now going to bring because it has been 20 years since we have been able to have this kind of thing to develop checklists, develop apps, to develop the ability for all of this to happen. Now we have this. We can move forward and really start to make this easier for everyone, patients and clinicians alike. People are worried, but really they do not see the incredible possibilities that are now going to come out of this work. It has just been individuals doing their best to make this easier, Rodney Grahame steering the process with the Brighton criteria, that a lot of doctors use, which is now no longer going to be used because we have these new criteria. A lot of people were not using that. They were using the old Villefranche. It just was a very mix-matched non-cohesive world that we were living in, that we really hope this will now help to order and fix.

If I was diagnosed in the past with hypermobile EDS, does this new classification mean I lose the diagnosis?

L. Bloom No. No one is saying you need to be re-diagnosed. You do not need to lose anything, and also, change your mindset from losing. Switched—it may be a switched diagnosis. If you do apply to research projects, or if you do go and visit your clinician to be reclassified, then potentially, they will then say that you may have HSD rather than hypermobile EDS. That is okay. That is not losing anything. It is gaining something that might actually help you get more management and care. That is what is critical here. We need to ensure that people are being managed, treated, validated, and diagnosed. We had to change things to ensure that happens. No one is losing anything. I hope that covers a lot of questions.

Given that hypermobility naturally decreases with age, as with secondary conditions, are you suggesting that these individuals will no longer be considered hypermobile EDS and they will then move into the HSD category (which is not believed to be a connective tissue disorder)?

C. Francomano Two things about that. I think the decreased of hypermobility with age is considered in the definition of the Beighton score and the Beighton cutoff with different ages. The committee recommended that a Beighton cutoff of four or more be applied to people over age 50. With regard to this consideration of a connective tissue disorder, I think the hypermobility spectrum disorders, we still have a lot to learn about the causation. There are going to be genetic studies looking at patients with those diagnoses. Some people will have hypermobility spectrum disorder because of other causes. I think many of the people with hypermobility spectrum disorders will represent hereditary connective tissue disorders as well. We still have a lot to learn about that.

How will we avoid further confusion by physicians with this spectrum table and avoid conversion disorder that so many are diagnosed with?

C. Francomano This is a challenge. I think it is important to recognize the comorbidities, the very many comorbidities that are associated both with the Ehlers-Danlos syndromes and with the hypermobility spectrum disorders. One of the most important things we can do with these publications is to establish that there is a bona fide relationship between gastrointestinal disorders, allergies, mast cell disorders, so many different issues that are associated with the Ehlers-Danlos syndromes and with the hypermobility

spectrum disorders. The fact that a person has a diagnosis of hypermobile Ehlers-Danlos syndrome or hypermobility spectrum disorder does not change the association with these various comorbidities. If physicians are willing to look and listen and learn, they will know that these things are—they are genuinely real and people need to be taken very seriously and treated appropriately for them.

When adding in the historical diagnosis, does that mean that someone who is diagnosed with hypermobile EDS may now be downgraded to HSD as they age and become less hypermobile?

L. Bloom Firstly, nothing is downgraded. It is a different diagnosis. It is not less than; that is very, very important for everybody to understand. It is not less than, it is equal. It is just different. I'll let Clair cover the changes with age.

C. Francomano I believe if somebody is diagnosed with the hypermobile type of Ehlers-Danlos syndrome and meets the diagnostic criteria for hypermobile EDS, say when they are 35 or 40, and then becomes less hypermobile as they age, personally, I would not change the diagnosis in their older years.

"At this time." What do you mean "at this time?" Does that mean at some point we will be required to be reevaluated? Also, isn't there a concern that doctors may begin to question if we were diagnosed by the old criteria or new criteria, and then not take a prior diagnosis seriously?"

L. Bloom The point of this is that everyone will take any diagnosis seriously. There were doctors not taking a hypermobile diagnosis seriously anyway. It is not like it was okay and we are now making things worse. The point of doing this is so that people outside of the people that really understand this condition do take it seriously. They are willing to diagnose it, but they are also willing to diagnose the HSDs, which need the same management and treatment as hypermobile EDS. That is what critical here. The consortium and the society and every other charity's job is for us to educate that. It is our job to make people understand that it is not less or more. It is not downgraded. It is not being put into something else. It is two different criteria, two different diagnoses, and both need the same attention, validation, management, and care. When we say "at this time," we cannot foresee a reason why people would be forced to be re-diagnosed. If you go to a doctor and they choose to reevaluate you, that is not something we can predict or control. Also, if you want to enter into the registry, you will be reevaluated based on the new criteria because that data is only as good as what you put in. We have to have new criteria in order for us to make the data very, very good. There are the issues that we have, and I do not think people should be scared that if it does come to a point where they are reevaluated, that that is a negative thing. If we do our job well, and we now have the tools to do it, then it will be seen as an equal thing and people get what they need.

Is it possible that you would not get a diagnosis of hypermobile EDS at a young age, but then as you get older and you get more complications, you would get the diagnosis?

C. Francomano Yes, it is very possible, because a young person may have generalized joint hypermobility without any of the musculoskeletal complications and those may emerge over time.

Were the neurological issues that are related to EDS taken into consideration for any of these classifications?

L. Bloom Yes. We have a neurology group that focused completely on all of these issues, but as we mentioned in the webinar, we have not included any of the comorbidities in the criteria. However, we have produced management and care guidelines because we are aware that they exist. We now need to prove the causation between these and prove the link so that we can then one day potentially include it in the criteria. Do you need to add to that?

C. Francomano No. I agree. We just do not have enough information at this point to really say whether the presence of Chiari, tethered cord, basilar invagination, if any of those things are fundamentally related to the Ehlers-Danlos syndromes, if they are causally related, if it is a comorbidity. We just need more information. We know we see them in patients who have these diagnoses and it is very important for us to recognize that they may be present—to look for them, and to treat them appropriately. We do not have enough information to consider them in the actual classification and diagnostic algorithm at this time.

For some time, it has been plugged that hypermobile EDS is not rare. Will hypermobile EDS now be considered rare and HSD more common?

L. Bloom Yes. You have heard me personally say many times “This is common. It is not rare. It is mis- and under-diagnosed.” The whole point of our mind is for it to change. We have to change our minds based on the work that has been done. By making the criteria stricter, less people will be diagnosed and it will go back to living in the rare disease category, which is around 1 in 5,000. We may do this registry and we may actually find out it is much more common than that. We won’t know. We do not know the figures yet. We do know that for sure HSD is going to be much more common and not a rare condition, but we cannot state figures accurately. We can guess, but it is not helpful to anybody. We need to now prove, and now we have the tools to enable us to do that.

Can we add our charity to the Amazon Smile charity program?

L. Bloom Yes. We actually are on there. We just need to do some things on our end because of the switch we had between EDNF and the society, and we are working on that currently. So, yes. Thank you for that question and please do add Amazon Smile. It is a really great way for you to help donate and support what we are doing.

Is this nosology saying that JHS and hypermobile EDS are not the same thing? In past research, it has been said that they are the same thing.

L. Bloom Yes. This is saying they are not the same thing and what is replacing JHS is HSD. We have had published papers, but things move on once work is done. That was the point of this effort.

C. Francomano I think at the time when people were thinking that joint hypermobility syndrome and hypermobile EDS were one and the same, the diagnostic criteria for the hypermobile type of

Ehlers-Danlos syndrome were not as well-defined as they are going to be moving forward. Under the understanding at that time, it certainly looked like hypermobile EDS and joint hypermobility syndrome were the same, but because of these new definitions, then we were able to separate them out.

Is there an umbrella term used to refer to the various EDS forms and the HSDs?

L. Bloom No. There is not. This is very new. One may come out, who knows, as time goes on. Currently, there is not an umbrella term.

C. Francomano I think our catchphrase Ehlers-Danlos Syndromes and related disorders would be a good umbrella term.

L. Bloom Yes, and that is as close to an umbrella term as we have for now.

Is there a way to get printed materials to distribute to the information to local health organizations?

L. Bloom Yes. As I said, all of these documents are free to download on our website and we want you to spread them as far and wide as you possibly can.

Why is the Beighton score being used when it was not intended to be used as medical diagnostic criteria?

C. Francomano The Beighton score has a very long history in the diagnosis of Ehlers-Danlos syndromes, and if you take a look at the paper, the committee that considered the Beighton score did an enormous amount of work. It is really an incredible effort to review all of the literature on the diagnosis of joint hypermobility. In the end, they felt that there really was not enough hard evidence to support including other joints into the diagnostic category that we think about for diagnosing generalized joint hypermobility, and that because it has been used so extensively, the Beighton score in its current form is our best tool for now. This is another one of those things that I think will certainly evolve over time. Many people recognize that by not including the shoulder, by not including the hips, by not including the craniocervical junction, we are omitting a lot of very important joints to consider in joint hypermobility.

When the criteria say first-degree relative is affected, does that mean within a specific time? I meet the classical EDS criteria; multiple first-degree relatives meet the hypermobile EDS criteria.

C. Francomano Usually we would expect to see within a single-family the inheritance of a particular type, one particular type in a family. The classical EDS criteria actually changed over time. I would say we really started to recognize that the extreme involvement of the skin is the definition that is going to correspond best with the finding of the type V collagen gene mutations. If this person met the classical EDS criteria some years ago, they might not meet the classical EDS criteria under the current recommendations. I think we would expect that the most likely thing is that within a certain family, within one family, the people with Ehlers-Danlos syndrome would all have the same type of Ehlers-Danlos syndrome.

Where can you get the papers to print?

L. Bloom You can get them through our website and they are free to download, and we encourage everybody to download them. It will be very easy to see on the homepage of our website. You will get everything you need, including updated pages on our website, answering questions that we have preempted you may ask. Please, at any time, email info@ehlers-danlos.com, lara@ehlers-danlos.com, helpline@ehlers-danlos.com with any questions, concerns, or things that you think should be on our website that you would find really helpful that we do not have on there yet. Help us. Let us know what would be helpful to you, because we are there for you.

The question is about the new musculocontractural Ehlers-Danlos syndrome. The person says that she tested positively genetically as well as the diagnostic criteria.

C. Francomano I am not the expert on the musculocontractural type and I am not the best person to discuss this, but if you take a look at the paper on the rarer types, of which Dr. Malfait is the first author, you will see all the current state of knowledge about that.

Is there a way to test for hypermobile EDS genetically or through blood tests?

L. Bloom No. There is absolutely no other way, other than clinical, that you can test for hypermobile EDS at this stage. No matter what doctors try and tease you with, or whatever papers you see out, or exciting promises—at this stage, there is absolutely no test for hypermobile EDS other than to be clinically diagnosed.

I do not quite understand how hypermobile EDS can be both under-diagnosed and over-diagnosed per video on the Society's website.

L. Bloom Honestly, it is unique. I believe that a lot of aspects of the EDS community are unique. One area is that this is definitely both over- and under-diagnosed. What I mean by that is patients cannot get to the doctor. They cannot wait on the waiting list, so they are going to “Dr. Google.” They are making assumptions based on what they read online, that they have the condition. They are telling people that. It might not be accurate. A lot of people are over diagnosing themselves and a lot of doctors are underdiagnosing the people who walk through the door. You’ve got a mixed problem, which is what has caused such confusion amongst the medical world and the patients. What we are saying is, stop diagnosing yourself and take the criteria papers to your doctors and demand that they use those to test you for this. You have to right to do that, and these are internationally agreed papers that are now in place to help doctors. It is criteria. It is not something that you would find on a forum or a charity’s website. This is not produced by The Ehlers-Danlos Society, or EDS UK, or any of the other national organizations. This is produced by the International Consortium on EDS and related disorders. It is produced by medical professionals, patient experts, that have all come together to work on this. It is something that can be respected and used everywhere.

C. Francomano I would also add that the Villefranche criteria, because they were so nonspecific, really contributed to the over diagnosis of hypermobile Ehlers-Danlos syndrome, because you could be diagnosed with hypermobile EDS in the presence of simple joint hypermobility, generalized joint

hypermobility without any of the other features of the syndrome, as it is being currently defined. I think some medical professionals were over-diagnosing it as well. Just as Lara said, it leads to really quite a lot of confusion and misinformation. I really hope that this new diagnostic set of guidelines will really help to streamline things.

What kind of research is occurring on pain management?

L. Bloom We get this question a lot as a charity because we have put out there that one of biggest priorities is research. The problem is that I genuinely have on my desk four or five research applications from people that are ready to go. That includes the registry that will equate to a lot of research. The problem is funding. People do not realize how much costs to carry out this work. People might donate \$5,000, \$10,000 and that is wonderful, but it won't make a dent in the research that it cost to put on this kind of project. The more money we have, and the more that we can get grants and the more that we can seek donations to do the research, then the research will be done. We know we need to do research into pain management, all of the comorbidities, the links, the causations, the prevalence, finding the gene, building the registry. There is an abundance of research that needs to be done. We have all of the professionals ready, in place, the labs, to do it. We do not have the money. We need to break out of the EDS community where we know there is not a lot of money, and make people outside care about this condition, and realize that they will probably know someone that is affected by this, and really try and increase the donations that are coming into the society, who have taken responsibility to try and make this research happen.

What about gastro problems? Are they now unrelated to EDS completely?

L. Bloom Absolutely not. No comorbidities are unrelated to EDS. What we are saying is that we cannot prove the causation. In fact, Professor Aziz's team in the UK has probably gone the furthest to prove the relationship between GI and EDS, but we have yet to prove why. What is causing that link? Until we do, it cannot be in the criteria. It is insane to me that people think we have ignored the comorbidities, when we equip groups that were just tasked with working out how to help people with these comorbidities to produce internationally agreed management and care guidelines. Even though it is not in the criteria, we are saying people with these symptoms, this is how you treat them. This is what we know. This is what we need to know. It is there for all of them—mast cell, neurology, GI, psychological, pain, physio, the Beighton. The list goes on, and for the next round, we are adding a pediatric group and a skin group. It will ever be increasing. Please do not think that we are neglecting the comorbidities, quite the opposite. We are giving them a lot of attention and time.

Can you please elaborate on the atrophic scarring criteria for hypermobile EDS? How do you determine it is not like true atrophic scarring?

C. Francomano Well, I believe it is true atrophic scarring. They are widened scars. They used to be described as cigarette paper scars. If you see a scar that is a thin line and it has healed well, and the skin has not separated out, that is not an atrophic scar. Maybe we could put some pictures of what atrophic scarring looks like on the website for people to see.

L. Bloom We can do that.

If a member of one house has diagnosed hypermobile EDS and a child in the same house has hypermobility spectrum disorders, what is the opinion of what is going on in this house?

C. Francomano Dr. Castori particularly addresses this issue in his paper. It is very possible that there will be children one who meets the criteria for hypermobile Ehlers-Danlos syndrome and another who has generalized joint hypermobility but no symptoms related to that generalized joint hypermobility. That child may be diagnosed with a hypermobility spectrum disorder. As we discussed earlier, as that child gets older, we hope not. We hope to develop strategies where people who are asymptomatic remain asymptomatic their whole lives and never need medical care for any of these comorbidities. A child with hypermobility spectrum disorder may develop more symptoms as they get older and then may eventually meet the criteria for hypermobile Ehlers-Danlos syndrome. Again, because we do not know what the genetic underpinnings for these conditions are, yet, we really cannot say on a molecular level exactly what is going on. Our fervent hope is that eventually we will have a molecular cause, a molecular test and will be able to test that child with hypermobile EDS and the child with hypermobility spectrum disorder, and say that they do or do not have the same alteration in their DNA that is leading to these findings in the connective tissue.

How will the society prevent doctors in the community from disregarding HSD altogether due to the belief that is simply a painless disorder that causes loose joints?

L. Bloom There is no belief of anything because up until today it did not exist. You are talking about joint hypermobility syndrome, and we have created the HSDs so that term is no longer used and that attitude and belief towards it also vanishes with it. The whole point of creating this paper, and what Castori has written in it, is HSDs can absolutely cause pain and all the comorbidities, and it stated clearly in that. If the doctor is diagnosing you with it, he/she needs to have read the paper and in the paper, it says that. People cannot make up their own belief of what something is. That is the whole point of having these internationally agreed papers so that doctors can actually use them and rely on them.

C. Francomano Also, in the spectrum of joint hypermobility, there is the asymptomatic joint hypermobility, and then there are the hypermobility spectrum disorders. The people with hypermobility spectrum disorders are specifically those who are experiencing symptoms related to the joint hypermobility. In the definition of hypermobility spectrum disorders is the presence of symptoms. We cannot—anybody who is saying that these are asymptomatic conditions just has not read the paper.

Can you speak to how skeletal deformities rather than musculoskeletal pain is factored into the diagnosis, for example, Marfanoid habitus?

C. Francomano The Marfanoid habitus is considered within the diagnostic criteria for the hypermobile type of Ehlers-Danlos syndrome. That includes the arachnodactyly, which is the relatively long fingers, as well as the arm span to height ratio of greater than or equal to 1.05. In my belief, there is probably a subset of patients with the hypermobile type of Ehlers-Danlos syndrome who have Marfanoid habitus.

Not everybody who has hypermobile Ehlers-Danlos syndrome has a Marfanoid habitus, but that is why in that list of criteria for the systemic involvement, we are able to pick five. Not everyone will have every one of those criteria.

Has any of the new research shown a link between the Ehlers-Danlos gene mutations and the MTHFR gene mutation?

C. Francomano Certainly there is no research linking any of the gene mutations that we know of, for the classical type and the vascular type with MTHFR gene alterations. Since we do not have a gene identified for the hypermobile type of Ehlers-Danlos syndrome we really cannot make a comment about that at this time. I will say that the MTHFR gene variants are extremely common in the general population. We would expect them to be extremely common among the patients with Ehlers-Danlos syndromes.

When do you expect the ICD-10 codes to be changed?

L. Bloom Impossible to say. We do not know how long that process will take. All we can say is we are working on it.

Is this the end of so-called “crossover” types?

L. Bloom I am not sure there ever were officially crossover types. Yes. You cannot have more than one type of EDS. I will let the medical professional elaborate, again, on that. We cannot seem to say it enough.

C. Francomano I think in the days where we were switching between types I, II, and III, and the classical and hypermobile type, people felt like there was that type II with minimal skin involvement, or maybe a little bit more skin involvement than we usually see in the hypermobile type, might have been considered a crossover type. There are also connective tissue conditions that seem to have features of Ehlers-Danlos syndrome and other connective tissue disorders like Stickler syndrome and osteogenesis imperfecta. I believe we have much more molecular information now and that crossover label is not appropriate anymore.

Are Tarlov cysts common in EDS patients?

C. Francomano The Tarlov cysts are cysts in the neuroaxis. They represent an expansion of the dural sac and the development of a cystic formation in the dura. They are relatively common in Ehlers-Danlos syndrome patients. They can cause a lot of neurologic symptoms and that is one of the specific neurologic conditions that is discussed in the paper on neurology and neurosurgical complications.

Can you elaborate about the tenascin-X?

C. Francomano There is a gene called tenascin-X that has been identified as causing a very, very small percentage of patients who carried a diagnosis of hypermobile Ehlers-Danlos syndrome in the past. It was less than 5% of a population of patients with hypermobile EDS were evaluated. Less than

5% of them had alterations in the tenascin-X gene. Those patients, we are now going to need to look and see. Do they meet the diagnostic criteria, the new diagnostic criteria that have been put forth for hypermobile Ehlers-Danlos syndrome? When we go forward, looking at patients with tenascin-X mutations, is there going to be a new set of diagnostic criteria that we need to develop specifically for those patients who have been molecularly defined?

L. Bloom It is 11 a.m. and I think we have reached the end. We kept cutting off on Facebook, so I am sorry to everyone there.

C. Francomano So sorry.

L. Bloom I would like to say to Facebook and to the webinar that this will be available on our website later today with all of the slides, all of the questions, and everything that we spoke through at the beginning. As soon as we have the link from the journal, it will be available to download on our website for free. We will be putting links and directions for people across all our social media platforms and on our website. Please continue to send in questions to info@ehlers-danlos.com or helpline@ehlers-danlos.com, or lara.bloom@ehlers-danlos.com and we will as a team try and get back to you. As you know, it is a busy time.

We have our press conference tomorrow, where we hope to get this message out to the wider world. It is a very exciting time and I would, again, like to reiterate that this is not a time for fear or panic. This is a time to be positive and to have faith that the best is being done to get everyone managed, treated, and validated so that we can all have the quality of life that we deserve.

I would like to say a big, big “thank you” to all of the members of the International Consortium. We would not have been able to do this without you giving up a lot of your free time, covering your expenses to fly around the world to do this and have meetings, cancel clinics, and do all the things that you have done to enable this to happen. Thank you to all the team at The Ehlers-Danlos Society for helping us get to today, and for all the other national charities that have supported this and the work going forward. Thank you to everyone. Thank you to everyone on Facebook for joining us, and everyone—we had over a thousand people joining us on the webinar. It is really amazing.

Now is our time.