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TRANSCRIPT - GR 04 25 25 **"The Hypermobility Syndromes - Ehlers-Danlos Syndrome and other Selected Heritable Disorders of Connective Tissue and Disability"** guest speaker Ina Stephens, MD from the University of Virginia

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Internal Medicine Grand Rounds

- All right, everyone. Thank you for being here. We're going to get started with our Department of Medicine Grand Rounds for the day. We're pleased to have Dr. Ina Stevens from the Department of Pediatrics with us, speaking about the hypermobility, syndromes, ehlers-danlos syndrome and other heritable disorders of connective tissue and disability. I'll take us through our Cme. Accreditation slides, and then Dr. Hassan will introduce our speaker, so our speaker's objectives and then no disclosures of note. And then today's session credit for faculty claiming C cme credit. I'll turn it over to Dr. Hasan.
- Well, good afternoon, everyone. It's my distinct pleasure to introduce our grand round speaker for today, Dr. Ina Stevens. So Dr. Stevens is a professor of pediatrics, pediatric, infectious diseases, and integrative medicine. Here at Uva she graduated from Wake Forest University School of Medicine, where she also completed her pediatric residency and served as chief resident. While there she completed her subspecialty fellowship in infectious diseases at the center for vaccine development at the University of Maryland.
- She was the principal investigator on multiple clinical, pediatric vaccine trials, including influenza Rsv. Meningococcus and dengue virus, and served on the Governor's Scientific Advisory Board for Pandemic, h. 1 n. One. Preparedness and response for the State of Maryland.
- She has particular interest in children with special needs and medical complexities. In addition to her roles in the Integrative medicine initiative, pediatric, integrative medicine, clinic and autonomic dysfunction clinic. She is the current interim medical director for the new Ehlers-danlos Center here at Uva. So we're very excited to have her speak with us today, so please join me in welcoming her.
- It's perfect great. Okay? Well, thank you all very much. So I want to kind of put this whole talk together about hypermobility syndromes, and I will tell you that I'm going to spend most of the time talking about the Ehlers-danlos syndromes. I think that that's probably what you're going to be seeing the most of, but obviously want to cover some of the other heterable disorders that you'll probably see, too, and kind of want to go over again. I have no financial disclosures.
- So let's just talk about like, what do I mean by the heterable disorders of connective tissues? What are they? So basically, it's a whole group of disorders. And there's multiple. But they basically include genetic disorders of the extracellular matrix. So you can only imagine your extracellular matrix is made up of multiple, multiple, different proteins, different, you know different cells, and any one of those in there having a defect or a deficiency can cause one of these connective tissue disorders. And so the problem is is that where is your extracellular matrix? It's all over your entire body. It is. Your entire body is made up of extracellular matrix throughout, so

any organ can be affected. Multiple organs can be affected, and sometimes it's very hard to kind of put it together, and the patient is presents is very medically complex. But one thing that almost all of them are characterized by are joint, hypermobility, skin, or vascular fragility and generalized connective tissue tissue friability. They don't have to have all 3. But most of the times they do.

- Okay, so these include the Ehlers-danlos syndromes. And I'm going to go over all of them. Why, we call them syndromes. And it's not just one thing, Marfan, syndrome, boy's deeds and hypermobility spectrum disorder. And obviously in the differential. For these are a lot of other, you know forms of multi-complex disease, including a lot of autoimmune disease, rheumatoid, arthritis, autoimmune, arthritis psorias lupus homocystineuria, you could go on and on, but these have to be in your differential before you kind of land on one of the heterobal disorders, connective tissue and screening labs and kind of your H. And P. Should get you to the point. You've screened out everything else, and I'm not going to go through how to screen all through that. You probably know that very well.
- So just in terms of the diversity of groups and the multiple different subtypes, you can only imagine that with every piece of your body being affected by connective tissue, they're very difficult to diagnose, because one person could go into the ophthalmologist because they have severe myopia in the back of their retina is kind of turning into Swiss cheese, like lacuna retinae, and another person ends up in orthopedics.
- The person ends up in Gi, and it's all basically based on the same problem. So it frequently goes undiagnosed in multiple subspecialty clinics and evaluations. And so the average length of kind of presentation to a doctor's office, and then to diagnosis for a patient. When any one of the heterable disorders of connective tissue is about 10 to 12 years.
- So you can only imagine going into like multiple different doctors, offices, subspecialty's office for 10 years, 12 years. And it's like, what's wrong with me. Why do I have so many problems? And it's often just not put together. So it's prolonged delay detected only after a long, long time some of the genetics. We know I'm going to go through it. And genetics is important. It's not vital, but it is important. And why is that? Because some of the subtypes have life threatening complications, obviously like vascular Ehlers-danlos, morphan syndrome, osteogenesis, imperfecta, etcetera.
- Okay, so the ehlers-danlos. Syndromes. Just to kind of go through them is number one in terms of these, heritable disorders. It's a group of about 15 known types. Okay, are there? More probably. But we know about 15 types have been identified, and 14 of them. And I have the plus in there, because there's been a recent kind of identification of one that's not yet on the genetic panel. It's but it's coming. So 14 plus types have been identified with a known genetic mutation. Hypermobile Ehlers-danlos is the most common type.
- And that's the type that we don't have any genetic diagnosis for. So that's a huge group that we're still kind of really investigating. So right now, hypermobile eds is diagnostically made by a clinical diagnosis. It's made by using the 2017 clinical criteria, and I'm going to go through those for you. But please know that there's a little outdated 2017 already outdated. And so genetic testing is available for all the other subtypes that we again know of.
- So things are, you know, still obviously evolving for the other types in terms of just the other heterobal disorders that I'm not going to spend too much time on. But I

want to just point out some key features. These include Marfan syndrome. Marfans, as you know, is autosomal, dominant. It is due to the Fbn. One gene. It's on chromosome 15. And this kind of encodes for Fibullin, which is in the extracellular matrix. And this you know, so problem with that all over the body. And this is just kind of a little.

- You know what some of the features are from morphans. I kind of liked it because it spells out morphans, and you can remember it easily. Lloyd's Dietz looks very much like Marfan syndrome, and there's 5 different types. All of them are autosomal, dominant. But 75% of them are spontaneous mutations. So you don't often find these necessarily in families. You may, because it's autosomal, dominant, but you can have a spontaneous mutation just as easily, and it affects the transforming growth factor, beta, which really regulates a lot of different things going on in the cells of the extracellular matrix. And it signals the extracellular matrix kind of working together. So again, very similar kind of connective tissue issues go on with both marfans and boys deeds.
- But one thing to remember with both of them characterized by aortic enlargement, aneurysms, and aortic dissection. So an aortic dissection does not necessarily mean this is Marfans, even though, if they look like marfans, genetic testing is really important because it could be Loy's deeds and other problems. Go along with that as well.
- Okay? And then kind of the last category, and I will spend a little bit of time on this, because it overlaps very much with elders, and those are just other hypermobility, spectrum disorders, and like, what does that mean? So I'll go through that. But bottom line is, there are a number of different subtypes, generalized, peripheral localized or even historical. So some of these older people, who are now very arthritic, for example, who said, Well when I was 20 I used to be able to do all those circus tricks kind of thing. So that's what I mean by historical hypermobility shares a lot of the features with more fans, heads, and Ehlers-danlos, but does not meet the strict criteria for any one of those. So. And the genetic cause again, is unknown.
- Okay? So going into the just Eds. Spectrum. One thing that is really important to know about it is each type of Eds kind of has their own little, you know, signs that seem to be really particular to that. So, for example, if you see kyphoscoliosis and they're really hypermobile, it's probably going to be kyphoscoliotic ehlers-danlos. It's probably not going to be vets. Okay, but there are a lot of shared features among all of them. So sometimes these patients can look very, very similar. And you may think. Well, I'm concerned about beds. I'm concerned about this. This may be classical type, and this would be, you know, if you start seeing some of these really ones on the outside, or even some of these on the kind of second periphery that would be a place to say yes, I'm a little concerned that maybe for genetic testing somebody who walks in with something like that. So somebody who maybe has, like, you know, multiple abdominal hernias or something like that with, you know, some pseudo tumors, molluscuma tumors. You may want to get genetic testing.
- Okay?
- So let's talk about why this is causing a problem. So the defects are in the extracellular matrix. And obviously this is just a very, very uncomplicated picture of the extracellular, much more complicated than that. And the defects involve all these different types of proteins, all mucopolysaccharideosis, all the other related molecules, and in all honesty, some of the problems with just that we're throwing

into the category for Ehlers-danlos syndrome. It's not just collagen. People. Just say collagen.

- Please remember that we don't only have one type of collagen, either. There's probably about 25 to 30 different types of collagen in the extracellular matrix. But problems are not just with collagen. In fact, classical Eds, the problem is with Tennyson that causes a problem with thecollagen down the line. But Tennyson is really the problem. So again, multi-system manifestations and the severity of how bad that patient's going to be how multi-complex that patient is going to be.
- You can't measure that. You can't find any kind of lab testing that's going to tell you that there's nothing that's going to say. This person is going to be worse off than that person, and you really don't know how the disease is going to manifest, or the syndrome is going to manifest throughout their lifetime. And that's really, really important to just kind of think about.
- Okay, just some other things to just kind of point out about the extracellular matrix. If they are predominantly having a problem with a certain type of collagen, you may be able to see that phenotypically. Okay. So if a child comes in. So I'm saying, child, I'm pediatrics. Just so, you know, I do see patients up to about 35 with Ehlers-danlos here at Uva. And I do see I have the occasional 60 year old who comes to me, too, for Eds, because just because, anyway, but bottom line if they come in. So if I have a child that's coming in. I just had a child last week who is very, very hypermobile, and we'll go over how hypermobile by the Baden score and a lot of other features! But he had 12 fractures just in his young life, and he's only 16 years old. So I'm like, Hmm! That kid's going for genetic testing because I'm concerned that he's got a type, one collagen defect could he overlap here with Oi and there is a lot of overlap of Oi with Ehlers-danlos, or could he have, you know, a stickler syndrome which a number of my patients actually turned out to have so sometimes little features, and how they present, and what they're presenting with can give you a little clue as to what type of collagen. And why? To get genetic testing, just the other thing to talk about of what is in this extracellular matrix looking very uncommon complicated here, because we're not really seeing all these fun little cells. But it's all the immune cells. So just you know, lymphocytes, mast cells, fibroblasts, other cells in the extracellular matrix that are definitely affected by disorganization. Disorders of, I'm going to say, collagen, please know it's many other proteins than that. But they are affected. And so about 20% of patients with Ehlers-danlos syndrome will go on to have at some point of their life an autoimmune disease.
- So at the very beginning, when I said, we kind of have to rule out a lot of those autoimmune disease, it still doesn't rule out that they may actually have an underlying hypermobility syndrome. They may just actually be at the point of their life where they've developed an autoimmune disease because it's very, very common.
- Oh, how am I going there it goes. Okay, so how common is Eds. And I put Hsd in here because I'll explain why hypermobility syndrome is sort of on the spectrum. Also of Eds. So right now it is considered, it's actually a lot more common than we think people used to, or actually still do. If anybody's looked at the Elo Sandler Society website. Does anybody know what it's? You know the big symbol of it is?
- It's the zebra right? And so the zebra, because we're all taught in medical schools. Don't look for the zebras. If you hear horse beats, it's not going to be the zebra, it's going to be the horse. Right? So don't even think about it. That's the rare thing.

- And so actually, the zebra is the symbol for the Ehlers-danlos society, because it used to be. This is so rare, or we're not thinking it's actually not that rare. Okay, so prevalence is about one in 2,500, maybe 5,000 for all the different subtypes and for hypermobile, it's actually more common than that. So these are something that you're definitely going to see. They're definitely going to come through the offices. They're going to come into. General you know, primary care practices. They're going to come into subspecialist office, and the problem is, they often go undiagnosed. So I'm going to kind of give you some clues as to where to go for them. And just so, you know the Comorbidities of all this all the Eds syndromes are very, very similar.
- Okay. But one thing that you I want to emphasize is that even if we diagnose an Eds syndrome in one member of the family the other family member, who obviously has the same joint hypermobility, can present completely differently. So, for example, I have a family where the mom is in heart failure because has a nice stretchy heart and went into heart failure with a lot of joint hypermobility. And the son has gastroparesis going on and on and on. So the syndromes can be very, very different, even within families. Okay? And why? We don't know that okay?
- And the problems can change over time. And that's 1 thing that I think is really important to know. So a child who is hypermobile is going to look very different from maybe their adolescent older brother look very different, maybe, from their parents or even grandparents, and the severity changes over time. So again difficult to diagnose and challenging to manage. Okay?
- So I kind of want to emphasize a little bit about why it's important to diagnose it. And why not to let? Why not let these patients go from doctor to doctor. They're still getting like their orthopedics problems fixed, or they're still getting their heart fixed, you know. Why can't they just do that.
- There's a lot of reasons not to. And one of the reason for early diagnosis, and why it's so valuable. It's to reduce the problems that can happen later on. And if anybody has been in a situation where they've been in fragmented medical care, it's very unsatisfying for the patient and it's really kind of in a lot of ways demoralizing for the patient. So so you kind of get rid of inappropriated and fragmented care, I think, is is really essential for these patients. You want to risk kind of psychological harm.
- I think that's huge. With a lot of these patients. They come in. And almost always there's a very big mental health component to it. We'll talk a little bit about that. Okay, so timely diagnosis can improve just how they're like living their daily activities of just like going to school, going to work, not having to be in a wheelchair, not having to wake up in chronic pain and obviously reduce risk of life threatening events, especially if we find one of the genetic subtypes.
- Okay, and this is one of the genetic subtypes. I want to highlight because a delayed diagnosis can be very problem. This is vascular Eds or Vets. And people will say, Oh, you know, there's definitely let me go back.
- I don't know how that happened, you know. There's definitely like a little bit of a phenotypic look to the face. I'm going to beg to differ. There's not okay. They look just like all my other patients. And I follow about 300 patients with Eds.
- There's no phenotypic necessarily face. So you can't say, well, this person looks like that, so I'm a little bit more worried. They can very easily slip through and slip under the, you know, under the rug, so you don't want to miss it. So anything that kind of gives you a little bit of a warning sign in the family history should prompt you to

maybe get this kind of genetic testing. So if there's been any arterial rupture, if there's a spontaneous colonic perforation, I have a family where, like you know, 12 year old had a spontaneous colonic perforation. That's a family where you get genetic testing for beds, you know any kind of fistula of family history of aneurysms. Another one is 3, rd trimester uterine rupture, which I think is really important.

- The problem is with beds is that even if it is kind of diagnosed early. There's not much you can do. I mean, we follow these patients. They're in our vascular medicine clinic. They're wonderful. But sometimes you can't avoid where an aneurysm may take place, and what kind of life threatening risk. So the life expectancy for beds patients is still about 48 years.
- Okay so just to kind of go over some of the diagnostic criteria for hypermobile Eds. And then when to say, Oh, I think I need genetic testing. I want to go over the 2017 criteria. I don't know if any of you know this 2017 criteria, I will tell you that these are being revised by 2026 to kind of include a few things. But one thing that I do want to emphasize about this is that I think it's really important for all doctors of all disciplines to kind of. Think about this checklist even if, like, you are like literally ent or ophthalmology, you know. Think about it. And if you're not going to do the full physical exam, refer them off to kind of do it because it's really important. And the patients really need to meet all 3 of the criteria to meet the diagnosis of Eds.
- So what are the criteria criteria? One is, they have to have generalized joint hypermobility, and this is kind of diagnosed with what we call a baton score. A baton score, looks at a number of different joints, looks at the elbows, the thumbs, the fingers, you know your knees, and things like that doesn't catch all the joints but a number of them, and then you say how many, and then it's positive. So for a child, a pre-pubertal child greater than 6 is fairly significant. That's because all children are fairly hypermobile.
- I mean, you know, we kind of call some of the poses that people that kids do like happy baby pose. You know, they can just like open up their legs, and they're just behind their heads. That doesn't mean that they're necessarily hypermobile. Children are hypermobile as they get older you become less hypermobile, so greater than 5 in a pubertal man or a woman up to the age of 50, is considered positive or greater than 4 out of 9, over the age of 50. And then, again, you can use some of the historical criteria, saying, I used to be able to do that, so to speak.
- So then, if they get to a criteria, and this is the baton sport.
- So this is kind of looking at the thumbs is looking at the fingers, knees. You know their lower back in there. This is basically giving you what the Bayton score is. And this is very. This takes 2 min to perform in the office. It's just part of your exam, and I think every you know, at least in primary care. This should be done on every patient, especially if they're coming in with complaints, you know. Multi system complaints. Okay?
- So that's criteria, one. If they meet criteria, one, let's go on to criteria. 2 criteria, 2. They have to meet
- A and B, or A, and C or B, and C, so they have to meet at least some combination of the 2. So criteria A has 12 different features to it, and you need to meet 5 out of the 12. So this is part of your physical exam. Sorry really.
- Okay. So here are a couple of them. You know, looking at their skin, looking at the hyperextensibility. I wanted to point out this picture. That's the Piezogenic papules on their feet, so you always make them take your Susan socks. So if I get down on the floor and I feel the bottom of their heels. And yeah, I feel them, and that

actually, if you know what this is that's little pieces of fat that's just kind of extruding out from their connective tissue. That's just kind of lacks at the lower face of their heel. So those are very characteristic and obviously multiple midline Hernias is a little bit of a red flag, and then you see the rest of them here, and here are some of the other features for feature A, and some of them are, you know, more echocardiographic, so you may hear a mitral valve prolapse. You may want to get an echocardiogram. Obviously no one's going to hear a little bit of a you know, in large a order, but that's certainly on the criteria. So if they have that as part of it as part of their workup that meets one of the criteria there, and so to meet feature A, you have to have 5 out of the 12 feature B is, you just have to have positive family history. You know, my mother was definitely diagnosed, or something like that. And so is it just, you know, Mom, or a sibling is really, you know not too far, much further than that 1st degree relative for meeting the criteria and then feature C. They must have at least one of these musculoskeletal pain daily for more than 3 months. Chronic, widespread pain or chronic recurrent joint hypermobility, subluxations, dislocations that go on without any trauma.

- Okay? And then criteria. 3 you have to rule out everything else.
- So you want to make sure, like their skin isn't unusually fragile. And it's definitely a classical Eds and things like that, or you know any of the other autoimmune conditions and things like that. At least you want to get a fine baseline workup to say that they've met a criteria. 3. And so if they're hypermobile and but not all 3 criteria are met. That's when they kind of fall into the category of that hypermobility, spectrum disorder or Hsd, so that's why it sort of heads. Hsd, because patients would come in with Hsd, and they let's say there's only 4 out of the 12 criteria you know, and nobody in their family has been diagnosed yet. I still have to diagnose them as an Hsd. But they're pretty close, so they're very much. The Comorbidities are very similar.
- Okay? And just to kind of go through that, not to go through this whole slide. But obviously, you can see that some of the major features are more common in the heads patients than they are for the Hsd patients. Okay, so I don't need to go through that. But they are a little bit of a difference.
- Okay, so why is genetic testing important? Who should go on for genetic testing? I kind of pointed a lot of that out, especially if you're seeing some of the really significant comorbidities. But this is what you can find in genetic testing. We can see some of the 14 other types of Eds or 14 types. And just so you know, there's
- 14 different basically types diagnosed. But they also could be due to multiple different genes and different problems. So it could be a problem with Tennyson which causes a problem with one of the collagen. So again, these 25 different genes encode for all these different kind of factors in the extracellular matrix.
- Okay? And not to look at it. Really, I hate obnoxious slides like this. But this is trying to give you an idea of the 14 different types, autosomal, dominant, or some Recessive, and the different types of genes, and they can all look again. Very, very similar. Okay? So that's just that's what we have so far with Eds, okay, but obviously still looking. And I'm going to go into that a little bit. So a lot of patients will come to us and say that they absolutely want genetic testing. And there's a lot of concern about this concern among geneticists. And a lot of it's because, again, the most common type hypermobile Eds, we don't really have a diagnostic genetic marker for, and we may come up with something else, and a lot of the times. We come up with variants of unknown significance and that makes the patients very,

very anxious. I have a Vus. I don't even know what that means. And so one thing to do, if you do have a vus, and to see if it is significant or not. And you want to know if it's near a pathogenic gene. One thing you can do is test other family members, especially those that are asymptomatic. And if you find the exact vus in a number of family members who are completely asymptomatic. Well, then, that Vus, even if it's right. Next to one of the genes that is known, it may not be significant, and that kind of calms. I think some of the concern down that there's a bus going on, but it takes a lot of effort. And so we don't always want to get genetic testing. So who do we get genetic testing. For what are the red flags?

- The red flags, you know, kind of what I talked about personal family history of some of these, you know really concerning medical events. You know anybody who's had a vascular dissection dilatation. Some, you know, the weird, recurrent fractures somebody who comes in with the 12 year old brother having intestinal perforation. That would be a good kid. That would be somebody to get on any kind of surgical complication, you know. Just recurrent dehiscence of wounds and things like that and obviously along with a combination of just everything else that we've discussed so far. But these are the people that I would send off for genetic testing with patients, I'd be more concerned about.
- Okay, so what are the comorbidities?
- How do these patients present? Well, I'm going to give you just like a two-page list that is not complete.
- But this is just kind of a flavor of some of the patients that will come in, and that I see daily, so they can come in with any aspect of joint or connective tissue abnormality. So they're just hypermobile, and everything hurts. They can have subluxation. Dislocations end stage arthritis really bad. Tmj, they'll say they wake up and their jaw is over on the other side, and they can't like unlock it and get it back.
- That's a warning sign. Okay? Anybody who comes in with pelvic floor dysfunction, you know, rectal prolapse, uterine prolapse. Everything like that or anything that looks like severe pelvic floor dysfunction, recurrent utis, urinary retention, urinary leakage, notwithstanding, having a number of different pregnancies, or something like that severe myopia, lacuna retin. So anything that really looks like the connective tissue is just not acting properly autonomic dysfunction. So autonomic dysfunction. I have a whole clinic just for autonomic dysfunction in and of itself so autonomic dysfunction can present almost as anything, because everything in your body is mandated by your autonomic nervous system. But for the most part, we kind of see a lot of the, you know.
- I hate to use this term. But pots. Okay, I don't like pots. Pots is really postural, orthostatic tachycardia syndrome is only telling us a little bit about that kind of orthostatic hypotension. But there are many other types of autonomic dysfunction that presents hyperadrenergic. They can come in with just chronic pain, and that could be autonomic dysfunction. So one of the most classic features for autonomic dysfunction to present with this severe occipital headache. Pain coming down the trapezius. Does anybody know what that's called?
- It's actually called coat hanger pain? Because it literally looks like you're wearing a coat hanger, and that's classic for autonomic dysfunction. So if you have patient coming in with that kind of complaint get their orthostatic blood pressures and just see where we're at. So it could be dealing with autonomic dysfunction and healing

the autonomic dysfunction or treating it. You really can't heal it very easily, but treating it can get rid of all their pain or a lot of their pain. So that's really important.

- Spinal instability, huge. So cranial. Cervical instability, tethered cord, occult tethered cord, and obviously things with pain. Chronic migraine, tinnitus, visual disservices and small fiber neuropathies.
- Small fiber neuropathy is seen in about 10% of patients with Eds. That's actually the classic number. But it's probably a little bit more than that. So small fiber neuropathy is very, very common.
- Some of the other comorbidities are allergic dysfunctions. Remember, those immune cells are all over the milk matrix. So I'm saying, mast cell, and I'm not the one who named it. Mast cell activation disorder. Please know. It may not just be the mast cell. There are other cells in there, including fibroblasts and other cells that release a lot of chemokines and a lot of other mediators that may be involved. But they can present with all these problems chronic urticaria, flushing rashes, hyperadrenergic pots. So a patient that's blood pressure goes way up. They have a big flush, and then they pass out because they're dizzy.
- You can't just say, well, it's because I had a low blood pressure.
- That's hyperadrenergic pots. And often the time it's caused by mast cell activation, gastric or mast cell activation and other cell syndrome. I hate again. I'm not going to just say mast cell gastrointestinal issues they can present to Gi. Clinic with any one of these complaints, and I'm sure sorry.
- I think I'm clicking this crazy, but those complaints are so common. I mean, most of your patients come in with that. So it's you know. It's not every patient, but it's definitely something to think of as gastric dysmotility. And the longer gastric dysmotility goes on, and the more and stage we're getting, the more damage we're developing to the vagus nerve and the more permanent these problems can be. So again, very important for early diagnosis pulmonary issues, spontaneous pneumotherapies, signs of asthma very, very common along with mast cell, and obviously the skin these patients often present to dermatology, you know, recurrent looking allergies what's going on with me so putting it all together, I think, is really really important. So these are just some of the Comorbidities.
- But I do want to spend a little time talking about mast, cell, and other cell activation syndrome, because it affects every tissue in your body. Your mast cells, and all the other front cells are all over your body, but especially your skin lungs, cns, and gi tract your mast cells, and I will just say mast cells, because it's easier to say, are up and down your Gi tract, and when they release and activate they can also cause a whole host of symptoms.
- They can exacerbate Gi. Dysmotility. They can exacerbate the pots and the autonomic dysfunction. So you have to kind of put it together and ask, so a lot of the times, I will say to the patient. Okay, so you are complaining about flushing all the time. Your face flushes, your ears flush. Do you get dizzy when that happens? Do you get nauseous when that happens. Do you get a migraine when that happens? And they're like, Yeah, you know. And so putting it all together sometimes can be really really helpful common triggers. For you know, things like mast cell activation.
- A lot. A huge one, I want to point out is temperature. So I will have patients that are fine, and they say, but I can't take a shower, because every time I go into the shower I break out in horrible urticaria horrible rash, and I faint in the shower. So that's really classic. Okay so why does this happen? All right? So just kind of

pointing out, you know this is the normal kind of close up look of that extracellular matrix. That's the mast cell. And this is normal collagen, normal kind of intact collagen. It's not doing anything. Well, when you have collagen that is defective, and I'm again just saying collagen could be many other things going on in there. I'm just shortening it up, saying Collagen. But that's kind of turning on the cell to activate and say, I'm releasing some extra atp extracellular atp release turns on mast cells that are right there. They're all intertwined, and the mast cells will degrade, and when the mast cells degrade and they release all, there literally can be hundreds of different chemokines and different mediators can wreak havoc in that area of the extracellular matrix, not just on the collagens, that there so it actually degrades, collagen even more so. We end up with a vicious cycle, with more hypermobility and more pain. But your autonomic nervous system is running on through. So you have kind of a mast cell kind of activation explosion in one area of your body, and it can definitely turn on symptoms of the autonomic dysfunction and other things. So you see how this kind of goes on. It's a vicious cycle. Once it starts happening.

- Okay, so these are just some of the mediators. These are the ones that we could actually test, for I left out. Tryptase tryptase is the one that we can catch in the serum if we're lucky. But all of these mast, cell mediators and other cell mediators are very, very temperature labile. So does anybody know how long Triptase actually stays alive in your serum after having a reaction.
- Let's like go to lab and get that serum tryptase. It stays in there for 11 seconds.
- So then it's gone. So serotryptase is. It's a nice baseline to get, because if you have mastocytosis and it's going on all the time, it's probably a little bit elevated, and we want to make sure we're not dealing with mastocytosis. But a normal tryptase level does not rule out that this is going on with potentially mast cell activation disorder the other mediators, histamine, Leukotrienes, and Prostaglandin. And you can kind of see a patient presenting a little bit differently, particularly Prostaglandins. Prostaglandins releasing all over the place causes pain you know. That's cool.
- Our ensys kind of get rid of that. So I mean, this is, you know, they tend to come in with a lot of migraine and a lot of abdominal pain when they're predominantly releasing prostaglandins. But you can find any one of these mediators in a 24 h, urine. You have to look for it carefully. It has to be collected carefully, but again, they're very labile. They may degrade, and it doesn't absolutely rule it out if it's you, don't find it there, but it's something to look for and these are just some of my patients with mast cell, and I just kind of wanted to point out a couple of interesting features to just. It's a little bit different than just flushing or just urticaria. And the main difference is, you see how well demarcated these are. I mean, it's like, very well demarcated.
- Okay? I mean, this one is extremely interesting, the way it's just well, very well demarcated. I can tell you that these ones over here 1, 2, and 3 were all from coming out of a shower, a hot shower. So again, just even coming out of the shower can present very differently in different patient. But that's a typical response.
- Okay so I kind of went over a lot of comorbidities. I kind of went over a lot of this stuff. And so this is how you may see a patient present with any one of these features. This is such an obnoxious slide. I'm not going to go through it, but it's anything they can come in with any complaint. So you really have to kind of think a little bit digging deeper through your differential and like before it's sent on off to a

subspecialist. But the 1 point I want to make a real point of is this is what you often don't see and a lot of the times you're just seeing like, well, they're coming in. They're doing okay. But there's actually a lot of pain going on. There's a lot of chronic pain and chronic pain or pain is very hard to see in somebody. You can't look at another person and say, I see your pain, or I can feel your pain, so it's very invisible. So it's a complaint that I think needs to be taken very seriously, because once you're in a pain cycle and your pain receptors are heightened.

- It's very hard to break that pain cycle. I'm sure you all deal with a lot of patients with chronic pain. I'm not going to talk about how I deal with chronic pain in my clinic and how I treat it. I have a lot of different modalities for it. But you want to kind of stop that from even starting. Okay? So the Chronic pain cycle is really concerning okay, and chronic pain goes along with a lot of other mental health problems. And the reason for that if you let's say you go to bed, and you're feeling okay. But in the middle of the night you actually dislocate or sublux your shoulder, you know, and you wake up with like a lot of pain, and then it's like a pain, and you're just in pain.
- That's very anxiety provoking. And then let's say you had a lot to do that day. Well, it's kind of depressing that you can't get out, and this kind of cycle just can keep on going. So just the whole, you know, chronic pain can lead to a lot of disability and a lot of decreased quality of life. So it's something I take very, very seriously.
- So how do we treat Eds? I'm not going to go very much into treatment. That's many more lectures. But one thing that I kind of want to say is that there's nothing curative. There's no curative treatment for any type. We don't have the magic bullet. I have so many patients that come in and say.
- Can I just take this great collagen that I just spent $100 on? And they swear it's going to make me feel better and like No, because your stomach's going to degrade it. It's not going to help you out. No, please don't buy expensive collagen and think it's going to really help you out. So the therapies are directed. It's not just collagen all the time. Anyway therapies are directed at just kind of preventing and mitigating impairment. Okay, so I am, as you know, I lead also the integrative medicine clinic as well as being an infectious disease specialist. And that's because taking care of medically complex patients has to be done. Integrative approach. You have to look at the whole patient. You have to look at their lifestyle, you have to look at what they're doing, and you have to work to heal them from the ground up. A lot of our treatments are Band-aids on their problems but healing them from the ground up cannot be emphasized. And how important that is. So, an integrative approach and focus on the whole person is something I really really want to emphasize. And yes, you need organ specific help.
- If they have a problem here, you need to send them to subspecialists. But really looking and focusing on the whole person, I think, is hugely important, and management involves all these things so kind of, and it extends throughout their whole life.
- So these are very complicated patients.
- Okay, so just some things to think about when you're in your office. If you see a patient coming with any one of these complaints here you know, you may want to perform the baton test. You may want to get a very detailed family history, and you may want to think about one of these disorders of connective tissue.
- And so these are just some of my patients. This is just some of the fun little party tricks they could do so want to talk just a few minutes. I have a few minutes left just to talk about the research that's going on in Eds, because there is a lot, but not

enough. And there's a little zebra sign. Okay, I'm pointing out this study because this was a real landmark study that just got a lot of notice in April of 2024, and this was published in June 24, th and this was done at the Norris lab down

- Russell Norris's lab down at Musc. They have an Eds center there that they're in the middle of building. They know them well, and Courtney Geissmer wrote this paper. But this was basically looking on whole exome sequencing on families, and 1, 97 patients that meet the criteria for hypermobile Eds. And they found a shared variant of Caliquinin 15 gene and so what they did is they took this gene. They put it in knock-in mice. So they made this Klk positive mouse model, and they followed them for a number of months, and they found that these mice actually developed symptoms of Eds. They had structural and functional connective tissue problems in multiple organs consistent with like how humans present. And so this was kind of a nice early step. But I think what they did was, you know, kind of looking at their, you know, electron micrographs. And microscopically, what happens to these mice? I just want to point out a few things. What they found out in the mice is that looking at their toes and looking at their feet, they yes.
- I am not good at this. Sorry they found what's called a higher strain, which means that it takes less pressure to cause a deformity. So they had a higher strain on their toe and a lower toe modulus, which means that it was just more friable and more flexible. So they klk positive mice were the blue mice. Were the blue lines here compared to normal. And then here were the positive mice looking at a sample of their connected, basically a tendon and their connective tissue. This is the negative mice, and you can see the positive mice. They're just kind of larger. There's fewer of them. There's spaces in between. And actually the length of the fibril were shortened in these mice. Okay they went a little bit further and did echocardiographic findings on the mice, and you can see that this is the knock in mice is the knockout mice. They showed Mitral valve prolapse in 5 out of the 6 mice, and the Mitral valve actually was thickened in myxomatous, and they also showed this on aortic valve leaflets and in the studies looking at the aorta, they showed some dilatation of the aorta in these mice. So this gene. The Klk. Is actually not on our genetic panel as of yet but this was just kind of published in June, and it's up and coming. So I think we'll be able to kind of screen for this subtype of Hds fairly soon.
- Other studies have been looking, and I kind of threw this all together. These are 3 different studies, but Rittelli and Chiarli work together. So these are kind of studies that have gone on together. But it's looking at extracellular matrix disorganization in patients with heads and Hsd and just widespread disarray of multiple different factors in the extracellular matrix has been shown in these studies and what they showed, which I just thought was very, very interesting. Was that so much of the disarray caused ongoing inflammation, and which is a vicious cycle, like what we talked about, especially when we talk about mast cells. But you don't only even have to have the mast cells there. The proteins in and of themselves can cause a lot of cellular disorganization. So these studies, lots of research going on in there and then the last major area of research that's going on is looking at different phenotypes of Hsd. So I mentioned that Hsd. Or hypermobile Eds is the most common type and they all can present very differently, and we may have found a Klk gene that is associated with some of them. So probably hypermobile. Eds is a whole bunch of different genetic, different subtypes. And so this kind of study looked at putting them into different clusters, with different types of phenotypes and

cluster. You know, for example, one and 2 have many more different issues their cranial cervical instability and spinal instability compared to cluster 3. And so studies looking at different phenotypes, and then looking at different genes, for that is really really important. But this study that was done on the phenotypes has what is what really has led to the development of making new criteria for diagnostic criteria for heads patients. So they're in the development right now of making the 2026 heads criteria. I think it's going to be very interesting. It's probably going to include a little bit more than the 2017 and have some variations, particularly on beaten score.

- Okay, and that just leads me to my very end here.
- I am very, very lucky, and I feel very excited to say that I received about 3 million dollars gift from a grateful patient to start an Eds center here. And so we're starting an Eds Center here at Eba. And the most important thing is getting everybody together and not having these patients be in fragmented care. So just want to tell you a little bit about the Eds center. My vision for the Eds Center is that it's actually going to be a medical home for those patients who live close enough and they will be followed here instead of most Eds centers. They go there. They get a diagnosis, and then they go back to Idaho.
- That would be not my liking, not the number. One thing I'd want to do. There are going to be patients that I'm going to do that because they're going to come nationwide. But if we can, we're going to give them an integrative approach of how we're going to treat them and try to heal them from the ground up and help them live with this permanent disability. We're going to increase the Eds literacy throughout their system. Here I am giving grand rounds, and we're going to be actually starting the opening of the center with coinciding with a research and clinical symposium that we're going to be doing. Probably in the fall or in the winter.
- We're going to be seeking certification by the Eds society. Right now there are about 21 centers around the world as a center of excellence for Eds. 12 of them are here in the United States. 3 of them are the Mayo clinic, so Mayo, Clinic, Jacksonville, Mayo, Clinic, Rochester, Mayo, Clinic, Arizona, Stanford, Johns, Hopkins, Musc is trying to get their certification. So just so, you know, they're kind of few and far between. So we're going to seek certification. And just so, you know, as I said when I was introduced. I am currently the medical director for the Eds Center. I am not going to take on the full job lots of issues. I have Eds myself and a lot of issues. So we have hired a new medical director. I'm very excited to say that he is. He's going to be joining your department. His name is Dacre Knight, and he just signed last week, and he's currently the medical director at Mayo Clinic, in Jacksonville, so he's coming to join us. So it's going to be really wonderful. But bottom line is
- You know, our center is gonna grow, or hopefully, you're gonna open in the fall.
- Maybe in the winter we'll see how it goes. Just the economics, you know, these patients are generally good payer mix, that's all that really says there. And we're going to be subsidizing faculty department. And so something that I'm just going to be kind of asking all departments is kind of look within your departments see who understands or sees these patients and wants to collaborate and wants to have more referrals. We're going to be sending more referrals your way. One thing that I should say about Eds, and I am a pediatrician, and I do see patients that are a lot older. It is because Eds is usually not diagnosed until after puberty.

- Okay, lots of reasons for that. But one of the main reasons is that estrogen and testosterone play a big role in joint laxity. So a little surge of estrogen. And all of a sudden we're very floppy. A lot of women and more testosterone. They tend to be a little bit less complex, when, as you know, so it tends to be a little bit female, heavy in terms of who presents as an adult. But again, they usually don't present until after puberty. So about 2 thirds of the patients that are in the system right now with Eds are over the age of 20.
- So they're going to be through internal medicine and through a lot of the medicine subspecialties.
- And that's just a picture of my family. We all have it. We're all very stretchy. And now I'm here to answer any questions. I'm sorry I went over 5 min.
- Tyson bell, and great thank you for coming. And I was just on a zoom, my wife and I, with Dr. Knight this morning talking about elementary schools and living in Charlottesville. So he's excited to come. From your experience, taking care of these patients. Coming to the adult side. What are things that you can anticipate. There might be issues that we need to be aware of things that we might put in order, and multi specialty care. What are some things you anticipate.
- So I can tell you a little bit about how the clinic is going to be formed, and we'll be. We're going to be having a multidisciplinary care clinic and the multidisciplinary pieces is obviously the primary care provider, both peds and adult. We are going to have genetics as one of the major stops, and we are going to be doing a lot of research, so every patient will be getting their blood drawn and put into a genetic repository that's asked over and over and over, and we'll discuss that whole. The Us. With everybody but the 2 other major components is getting them a physical therapy evaluation and I'll explain why. And the second, the last piece of it is psychology. So what I see a lot in the adult patients is that they have been hurting, hurting, hurting, dislocating, and more hurting, and the older they get the more wheelchair bound they become. So I see a lot of adults in wheelchairs, or they come to me wanting wheelchair or more disability.
- And so we've talked a lot about the problem is, you know, we can't fix this problem, and a lot of the problems at least, just like with the orthopedic problem is that you can't really strengthen a ligament or a tendon, you know, and the looser they get the bones just kind of go like this, and they flop around, and then they bang, and then we get really bad arthritis. So all you can really do is strengthen the muscle to hold on to your joint for dear life.
- And so a lot of these patients are such such pain so disabled they it's like they've gotten to a vicious cycle of sitting on the couch and not exercising. So I see a lot of patients that are very, very deconditioned. The older they become, the more deconditioned they are with a lot more joint problems. And I see more of the end. Stage problems like I mentioned about the vagus nerve becoming more damaged. So more gi problems. But what I, what I see almost in every single adult, less so than in the children. And this may just be an aspect of being kids is the psychological impact this had.
- They've gone from doctor to doctor to doctor a lot of times they come in, and they'll say, like, you know, they they almost have a barrier up of like, what are you gonna say to me. Are you gonna kick me out of the office?
- I it's it's really. I see a lot of. I don't want to use the word Ptsd, but there's there's some serious medical Ptsd, I see a lot with the adults, and I think that has to be

addressed, and then really kind of healing them with conditioning physical therapy and giving them home. I think that's really important.

- Thank you. Yeah thank you so much for this very exciting to hear about the new center coming. So I have my own question and a couple of questions in the chat. My question is more so. Just about our population here. How large is our Eds population? Are we seeing a lot of folks already from other states? And you know, what are some of the just like basic demographics of that population just to have a sense of who to look out for.
- So in my clinics. And I say my clinic. So I run the integrative medicine clinic, the autonomic dysfunction clinic, and the diagnostic dilemma clinic. So kind of putting those all together. I follow about 300 patients with hypermobility spectrum whether it's Marfans Eds, or you know. So they all kind of fit into that. I know that right now there's a waiting list for the Eds Center to open of over 100 patients just on the waiting list for waiting for the center to be open. And those are patients over the age of 35 right now. My patients are coming from, I would say, like the Tri-state area. So
- North Carolina, West Virginia, all over the State of Virginia all over. I have some patients coming from Jersey, Pennsylvania. So they they're, you know. They're they're coming. There's just, you know, but mostly within a 5 h driving distance, but definitely from different states for sure.
- And then question from Jack Foggs in the chat, can you quote rule out vascular eds with genetic testing. I never know how aggressive to be with imaging. For instance, an Eds patient has neck pain could always be a dissection. Should I keep ordering the ct. so I missed the 1st part. Can you rule out vascular Eds with genetic testing? Was the 1st question. Yes, yeah. So vascular eds can be ruled out by genetic testing. So if you do see somebody with a concerning kind of one of those features that I mentioned, any kind of dissection, a rupture of intestine or history of that or a family history of that I would especially if they're hypermobile. I would send them off for genetic testing, because that one we do have genetic testing for, and if we find that they have beds then almost always I co-manage them with vascular medicine and vascular medicine watches them, you know, closely, and but sometimes it's hard to predict what's going to rupture. So they still have a shortened lifespan.
- Yeah. And then the second part was just about how aggressiveness with ordering a Ct. It's like a patient with vascular Eds is having like neck pain or something to rule out dissection.
- So I mean, I think that's a good question. I think that you know.
- I think that if you really had a patient with beds, and they were diagnosed with beds, and they're coming in with worsening neck pain. I would probably not necessarily waste my time on the Ct. I would call vascular medicine. Say I want an arteriography, or like I want, you know. Vascular look at an Mriv, you know, Mrv.
- I think that would probably be what I'd be, you know, but there's so many other things in the differential, too, you know. So you really have to do a full physical like, for example, if they're giving you tingling in an arm, or they're having problems, you know, bladder or bowel control, or something like that. I'd be like, Okay, is there cranial cervical instability that could be signs of a tethered cord from down here. So the differential is really really huge. I probably would alert the vascular medicine. As to I am concerned, you may want to get this study as well, but I would start looking also for other things because it's probably it's quite possibly not just a dissection. Yeah. And then last question in the chat is just where's the center going to be located?

- It looks like right now. It's probably going to be in the 500 building of Fontaine, where it's we're probably starting there. There's talk about where it's going to. We don't have it's it's going to start out small, but we know it's not going to have enough space, so probably at 500 for now.
- Thank you so much for the talk. This might be last question. Just based on our time since you started out, you said, Pete's id tell me I I'm just interested about you. Certainly by the talking today or not pigeonholed in one particular specialty. Just for a lot of our residents who are interested in going into a specialty. What has your journey been like broadening your kind of your, the way you approach problems from not just one specific specialty to thinking about patients a little bit more broadly. And what can that say about like multidisciplinary care?
- That's a great question. Thank you. I think Pete's id kind of gave me the framework of how to start evaluating these patients. And the reason for that is, and yes, I did 20 years of vaccinology. So I did sort of specialize a little bit in id. But Id is a field that involves everything.
- So it's not just not just the heart. It's not just this. You can get an infection everywhere, and what I always say to our residents and medical students on the id rotation is that your job on this rotation is to be a detective. You are a detective. That is what your job is. You just got to have to have that differential like, if you're thinking fever, what's my differential? And so and then you have to ask the guided questions and narrow it down and narrow it down. So it's like you have to do a guided H. And P. To get that. Oh, I came up with the diagnosis and to me that kind of thinking, I think, is what has made this very accessible for me, and I've done training over the years. So, besides being, you know, integrative medicine certified and doing integrative medicine, which is very much of like to me. It's not alternative. It's just another toolbox you know. It's just a you know. I teach them deep, diaphragmatic breathing to help quiet down their sympathetic tone, you know, instead of 1st step putting them on an Ssri or something like that. But just for example, it's just a bigger toolbox.
- But I'm also a certified yoga teacher. I'm a certified yoga therapist, and I'm a personal trainer, and I have a lot of all that training as well. And so it was kind of like I was able to kind of put these together. And I'm looking at these patients.
- And I kind of did the same detective work. So I think you really have to look at the whole patient as a whole. I loved Id for that reason it was not exclusionary of anything. So maybe that's just kind of how I got into the field, and the other main thing in terms of seeing a lot of these patients. Besides integrative medicine is. I also see all the patients with long covid.
- So as id specialists in autonomic dysfunction, as you know, most patients with long Covid have autonomic dysfunction and a lot of patients with long covid and autonomic dysfunction happen to also be hypermobile. They are at highest risk for developing long Covid, much more so than the general population. So by default, I started getting a lot more patients from that as well.
- Well, thank you for the time.