What to do when you suspect Ehlers-Danlos syndrome

a practical guide

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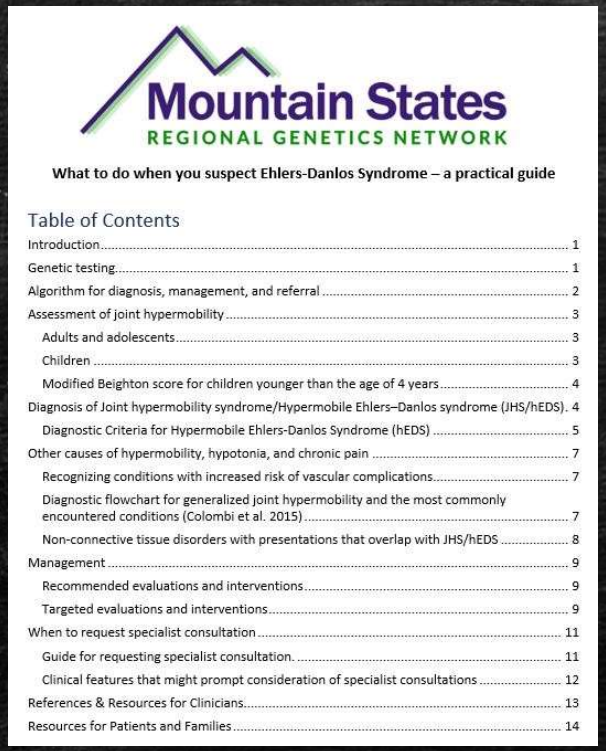
Scope



Mountain States
REGIONAL GENETICS NETWORK

What to do when you suspect Ehlers-Danlos Syndrome – a practical guide

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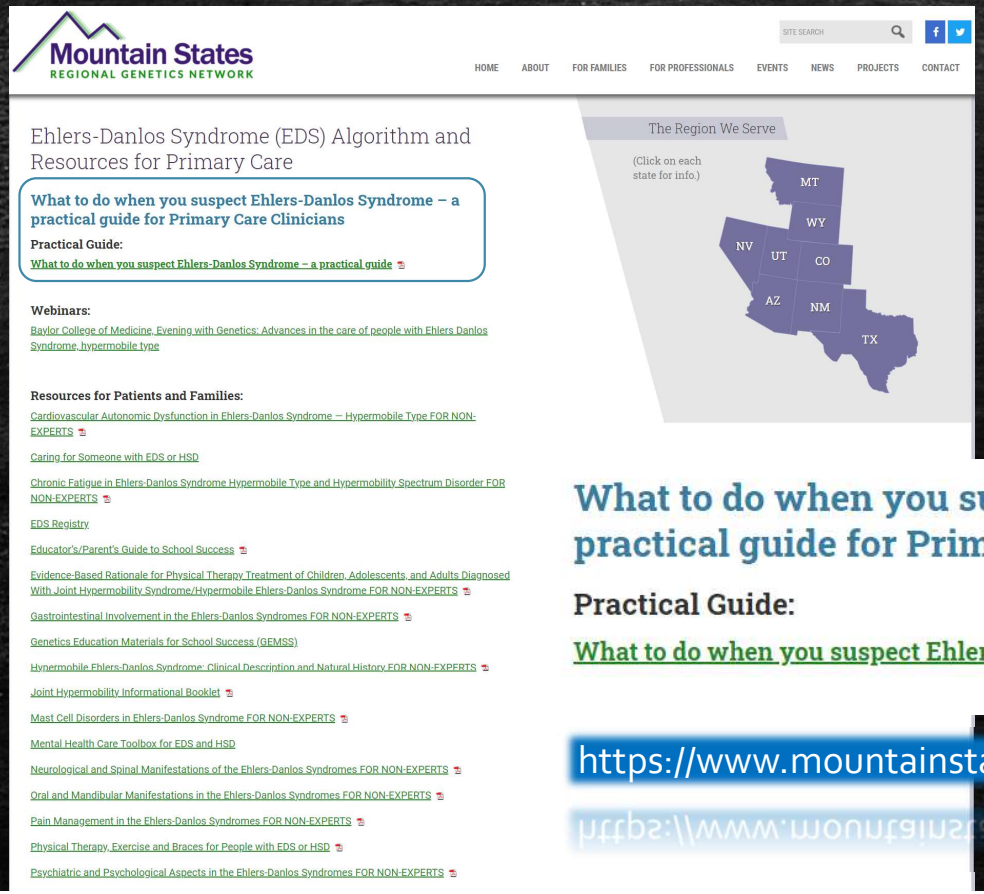
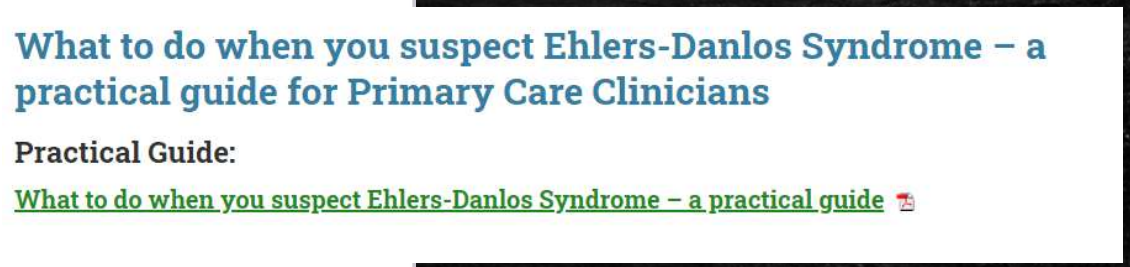
- Resource for pediatric health care providers
- Focus on **Joint hypermobility syndrome/Hypermobile Ehlers–Danlos syndrome (JHS/hEDS)**, also called **hypermobility type EDS**, formerly known as **EDS type 3**

Where to find the practical guide





https://www.mountainstatesgenetics.org/projects/eds-algorithm/

Acknowledgement

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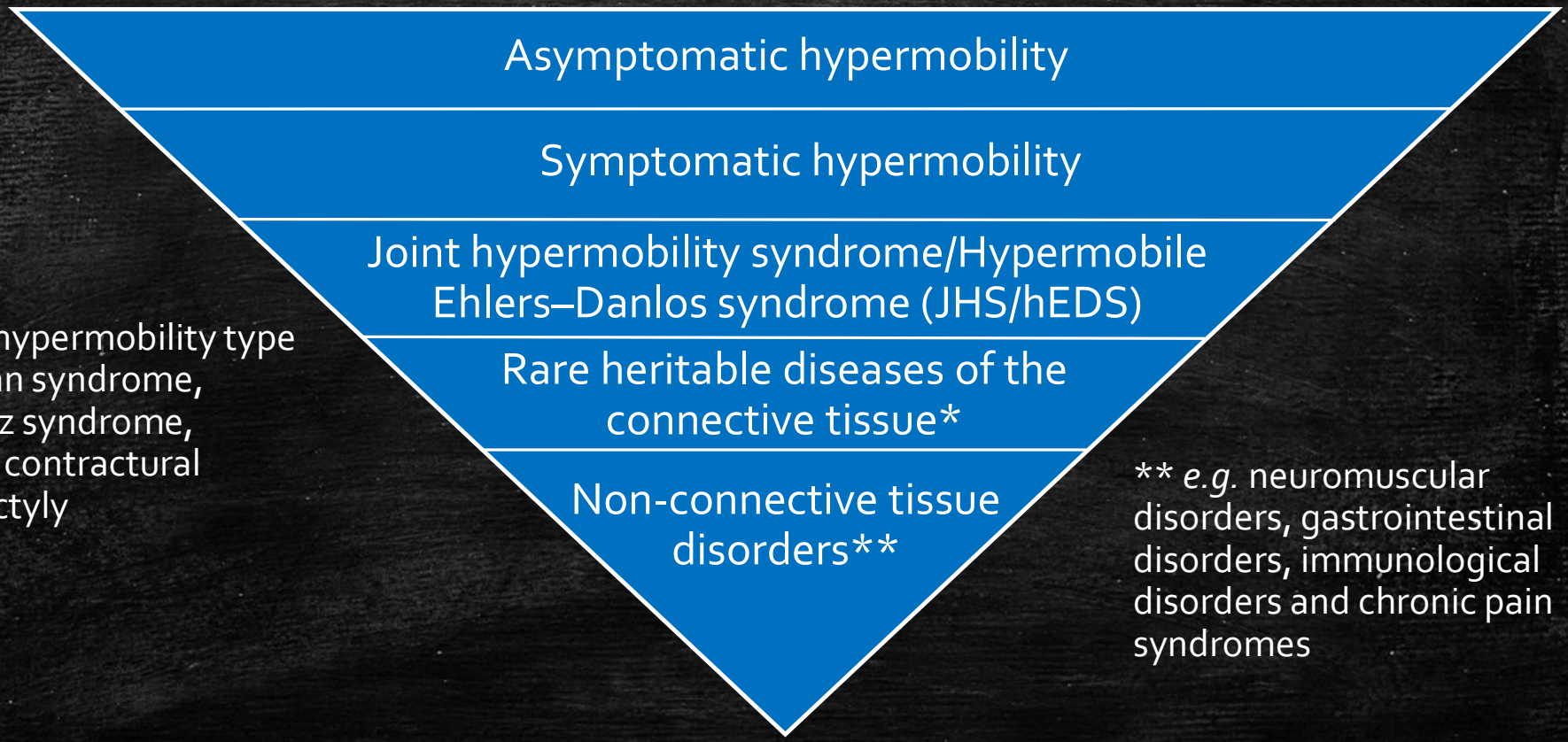
Introduction

- Joint hypermobility (JHM) is defined as a more than normal range of movement in a single joint or generalized.
- Prevalence of asymptomatic JHM in children may be more than 30%.
- Generalized joint hypermobility (GJH) is estimated to affect 10 to 20% of the general population.
- ***Most cases of JHM you see in your clinic will be an isolated phenomenon, defined as asymptomatic hypermobility.***

Terminology

- Joint hypermobility (JHM)
- Asymptomatic *versus* symptomatic JHM
- Joint hypermobility syndrome (JHS) =
  Ehlers-Danlos syndrome – hypermobility type (EDS-HT) =
  Hypermobile Ehlers–Danlos syndrome (hEDS) ⟶ JHS/hEDS
- Rare heritable diseases of the connective tissue
  - Non-hypermobility type EDS (13 of 14 are molecularly defined; includes classic type, vascular type, arthrochalasia type, dermatosparaxis type, kyphoscoliosis type, etc.)
  - Marfan syndrome (FBN1)
  - Loeys-Dietz syndrome (TGFBR1, TGFBR2, SMAD3, TGB2, TGF3)
  - Congenital contractural arachnodactyly (FBN2)

Joint hypermobility (JHM)



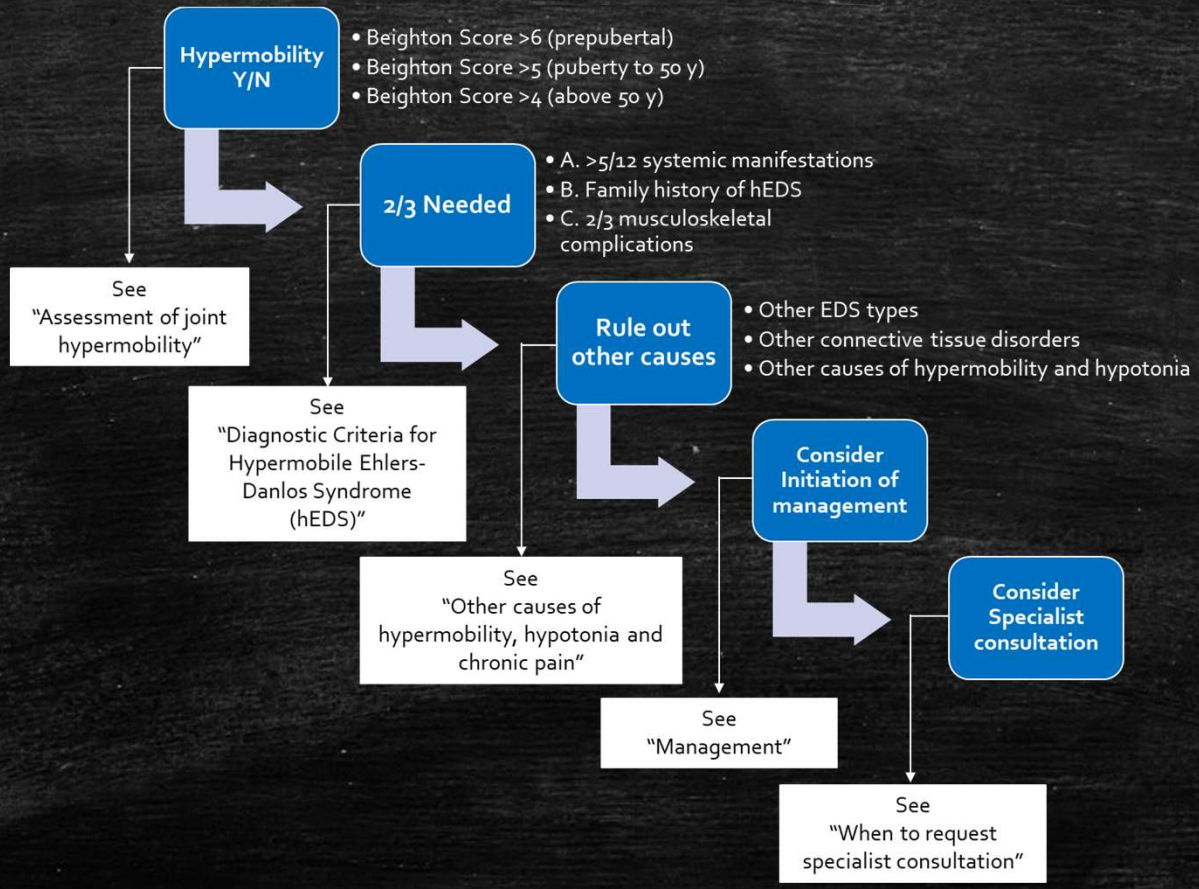
* *e.g.* non-hypermobility type EDS, Marfan syndrome, Loeys-Dietz syndrome, Congenital contractural arachnodactyly

** *e.g.* neuromuscular disorders, gastrointestinal disorders, immunological disorders and chronic pain syndromes

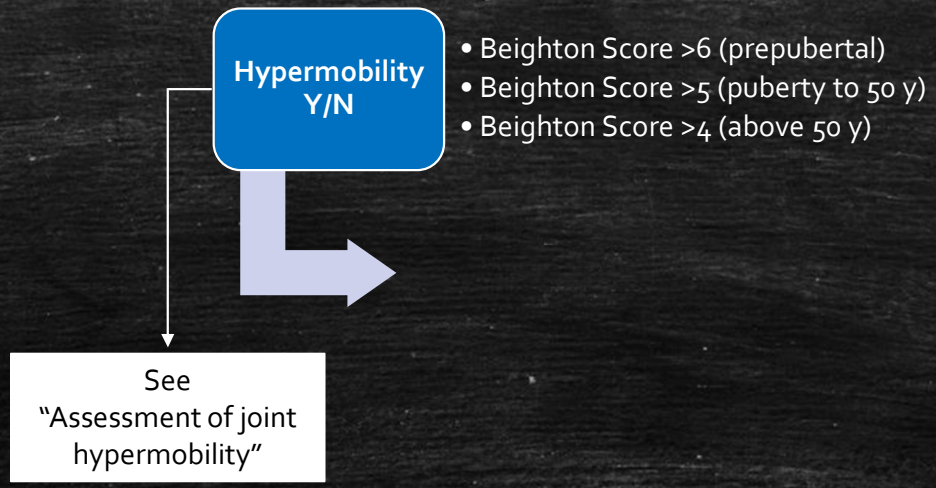
Genetic testing

- The scope of this practical guide is JHS/hEDS.
- There is currently no genetic test available for JHS/hEDS, and the diagnosis is made clinically.
- Genetic testing is available for 13/14 types of EDS and plays an increasing role in the classification and diagnosis of heritable connective tissue disorders.
- Genetic testing will be recommended if indicated by findings on physical exam, medical history, or family history.
- Genetic testing ideally is initiated in collaboration with a health care professional versed in the diagnosis of heritable connective tissue disorders.
- Genetic counseling should be provided if testing is pursued.

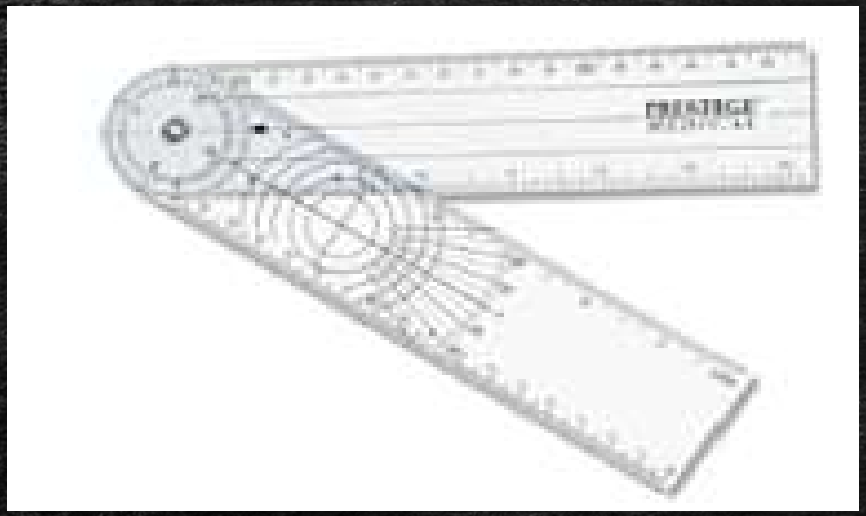
Algorithm for diagnosis, management and referral



Assessment of joint hypermobility

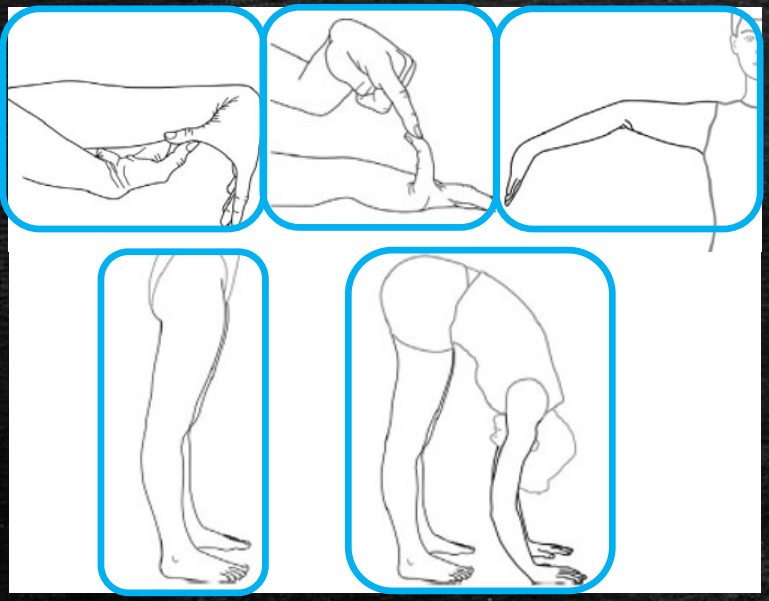


Goniometer for assessment of hypermobility



Hypermobility is best assessed using a goniometer according to the Beighton Scoring system

Beighton scoring system for hypermobility



Beighton Score (BS) is a 9-point score with one point for :

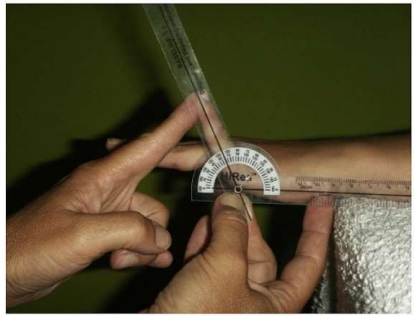
1. Passive apposition of the thumb to the flexor aspect of the forearm (one point for each hand),
2. Passive dorsiflexion of the V finger beyond 90° (one point for each hand),
3. Hyperextension of the elbow beyond 10° (one point for each arm),
4. Hyperextension of the knees beyond 10° (one point for each leg),
5. Forward flexion of the trunk with the knees extended and the palms resting flat on the floor.

Passive apposition of the thumb to the flexor aspect of the forearm

one point for each hand

Smits-Engelsman B, Klerks M, Kirby A. Beighton score: a valid measure for generalized hypermobility in children. J Pediatr. 2011 Jan;158(1):119-23

Passive dorsiflexion of the V finger beyond 90°



one point for each hand

Test position	Motion tested	Positioning Goniometer	Anatomical landmarks	Method
Sit on chair at the short side of the table with arm in 80° abduction, elbow flexed 90°, forearm resting on table, forearm pronated.	Passive Dorsiflexion Digiti 5.	MCP 5.	Dorsal side Metacarpalia 5; in the length of Digiti 5.	Lateral method.

Hyperextension of the elbow beyond 10°

one point for each hand

Test position	**Motion tested**	**Positioning Goniometer**	**Anatomical landmarks**	**Method**
Sit on chair with shoulder 90° anteflexion, forearm supinated	Passive hyperextension of elbow.	Lateral epicondyl Humerus.	Humurus pointed at tub major humeri; Radius pointed at proc styloideus.	Lateral method.

Hyperextension of the knees beyond 10°

one point for each hand

Test position	Motion tested	Positioning Goniometer	Anatomical landmarks	Method
Lying backwards with legs in horizontal position.	Passive hyperextension knee.	Lateral femur epicondyl.	Femur pointed at trochanter major; Fibula pointed at lateral malleolus.	Lateral method.

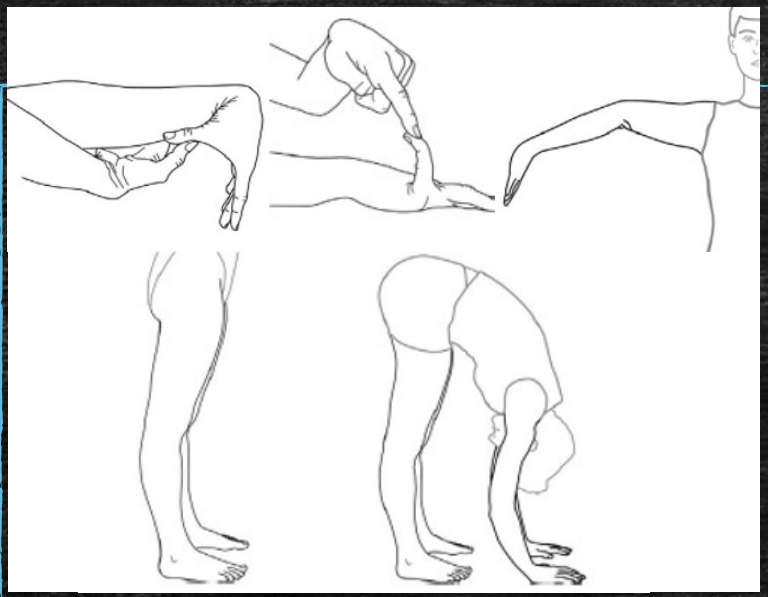
Forward flexion of the trunk

Score: Positive

Score: Negative

one point

Beighton scoring system for hypermobility



Maximal BS: 9

Positive BS:

Beighton Score ≥6 (prepubertal)
Beighton Score ≥5 (puberty to 50 y)
Beighton Score ≥4 (above 50 y)

Description	Bilateral Testing	Scoring (max. points)
Passive dorsiflexion of the fifth metacarpophalangeal joint to ≥ 90 degrees	Yes	2
Passive hyperextension of the elbow ≥ 10 degrees	Yes	2
Passive hyperextension of the knee ≥ 10 degrees	Yes	2
Passive apposition of the thumb to the flexor side of the forearm, while shoulder is flexed 90 degrees, elbow is extended, and hand is pronated	Yes	2
Forward flexion of the trunk, with the knees straight, so that the hand palms rest easily on the floor	No	1
Total		9

Is the Beighton score valid in children?

Yes!

"The Beighton score, when a goniometry is used, is a valid instrument to measure generalized joint mobility in school-age children 6 to 12 years. No extra items are needed to improve the scale."

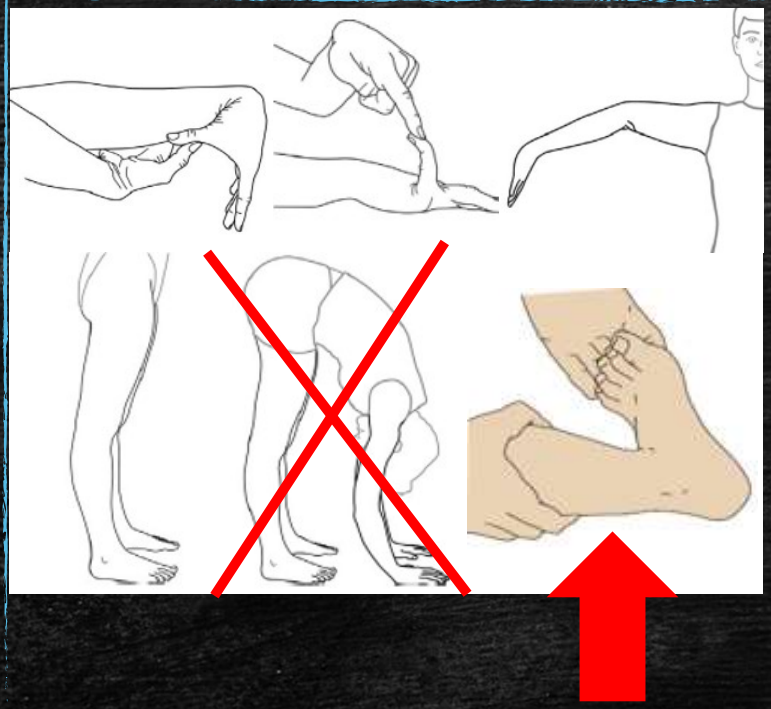
Smits-Engelsman et al., J Pediatr. 2011 Jan;158(1):119-123

In contrast,

- Pain over a period of time or after exercise does not add valid information to hypermobility related complaints in children under 13 years.
- Hypermobility (Beighton 6/9) was not predictive of future musculoskeletal pain in preteen and adolescent children

El-Metwally et al., BMC Musculoskeletal Dis 2007;23:8-46

What about preschool-age children?



"Forward flexion" is difficult for children younger than the age of 4 years.

It is replaced by passive dorsiflexion of the ankle joint bilaterally.

Positive when the angle is >30° (bilateral testing = 1 point for each side).

Total BS: 10 (!)

Positive BS: 6

Romeo et al., J Pediatr. 2016 Sept 176(1): 162-166

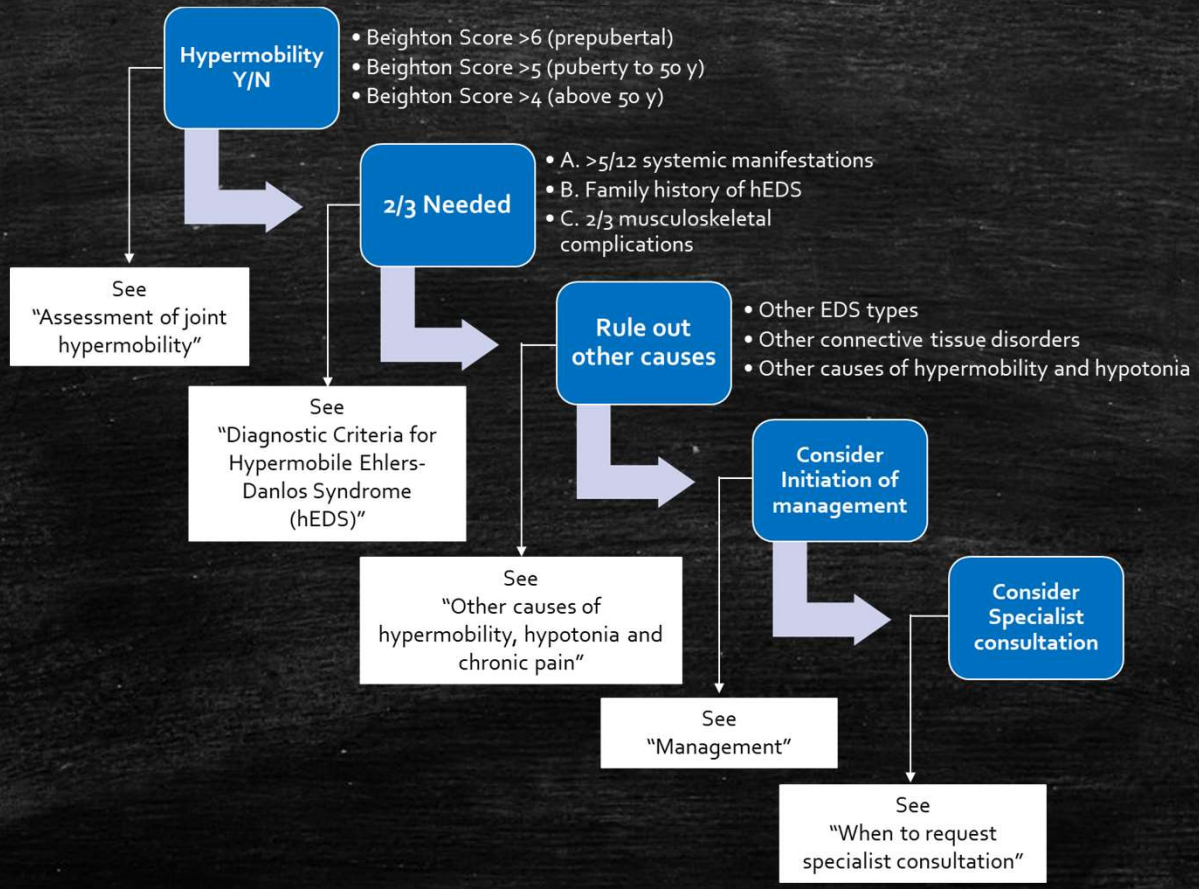
Limitation of hypermobility as a clinical diagnostic criterion

- Hypermobility in heritable connective tissue disorders other than JHS/hEDS may not always be the presenting sign and may even absent in several important differential diagnoses of JHS/hEDS.
- Vascular EDS (vEDS): hypermobility is not generalized, but typically limited to the distal/small joints and is not usually associated with dislocations or subluxations of large joints or may be entirely absent.
- Marfan syndrome: Joint hypermobility is not part of the systemic score in the revised Ghent criteria for Marfan syndrome.
  - A positive wrist and thumb sign in patients with Marfan syndrome may reflect dolichostenomelia (long limbs) rather than hyperextensibility of joints and ligaments and may be associated with reduced extensibility in the elbow, a criterion in the systemic Marfan score.
- Beighton score may be misleadingly low in a patient with hypermobility affecting mostly large joints.

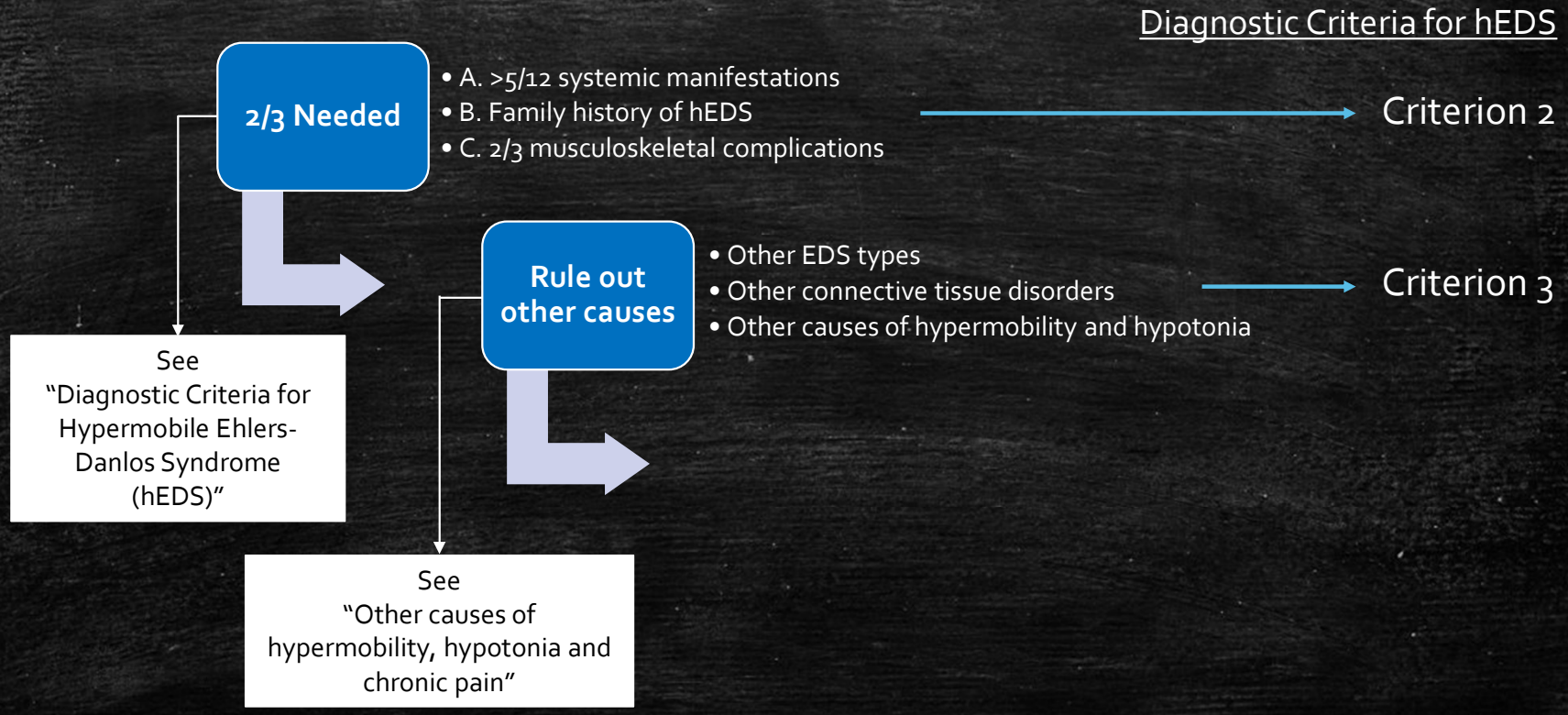
Assessment of joint hypermobility

Now that we established hypermobility, what's next?

Algorithm for diagnosis, management and referral



Diagnosis of Joint hypermobility syndrome/Ehlers–Danlos syndrome hypermobility type (JHS/hEDS)



Diagnostic Criteria for Hypermobile Ehlers-Danlos Syndrome (hEDS)

The clinical diagnosis of hEDS needs the simultaneous presence of *criteria 1 and 2 and 3* summarized in the table

Diagnostic checklist accessible on the website of the EDS Society:

https://ehlers-danlos.com/wp-content/uploads/hEDS-Dx-Criteria-checklist-1.pdf

1

2

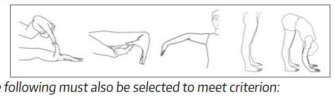
3

CRITERION 1 – Generalized Joint Hypermobility

One of the following selected:

- ☐ ≥6 pre-pubertal children and adolescents
- ☐ ≥5 pubertal men and woman to age 50
- ☐ ≥4 men and women over the age of 50

Beighton Score: _____/9



If Beighton Score is one point below age- and sex-specific cut off, two or more of the following must also be selected to meet criterion:

- ☐ 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?
- ☐ Do you consider yourself "double jointed"?

CRITERION 2 – Two or more of the following features (A, B, or C) must be present

Feature A (five must be present)

- ☐ Unusually soft or velvety skin
- ☐ Mild skin hyperextensibility
- ☐ Unexplained striae distensae or rubae at the back, groins, thighs, breasts and/or abdomen in adolescents, men or pre-pubertal women without a history of significant gain or loss of body fat or weight
- ☐ Bilateral piezogenic papules of the heel
- ☐ Recurrent or multiple abdominal hernia(s)
- ☐ Atrophic scarring involving at least two sites and without the formation of truly papyraceous and/or hemosideric scars as seen in classical EDS
- ☐ Pelvic floor, rectal, and/or uterine prolapse in children, men or nulliparous women without a history of morbid obesity or other known predisposing medical condition
- ☐ Dental crowding and high or narrow palate
- ☐ Arachnodactyly, as defined in one or more of the following:
  (i) positive wrist sign (Walker sign) on both sides, (ii) positive thumb sign (Steinberg sign) on both sides
- ☐ Arm span-to-height ratio ≥1.05
- ☐ Mitral valve prolapse (MVP) mild or greater based on strict echocardiographic criteria
- ☐ Aortic root dilatation with Z-score >+2

Feature A total: ____/12

Feature B

- ☐ Positive family history; one or more first-degree relatives independently meeting the current criteria for hEDS

Feature C (must have at least one)

- ☐ Musculoskeletal pain in two or more limbs, recurring daily for at least 3 months
- ☐ Chronic, widespread pain for ≥3 months
- ☐ Recurrent joint dislocations or frank joint instability, in the absence of trauma

CRITERION 3 – All of the following prerequisites MUST be met

1. Absence of unusual skin fragility, which should prompt consideration of other types of EDS
2. Exclusion of other heritable and acquired connective tissue disorders, including autoimmune rheumatologic conditions. In patients with an acquired CTD (*e.g.* Lupus, Rheumatoid Arthritis, etc.), additional diagnosis of hEDS requires meeting both Features A and B of Criterion 2. Feature C of Criterion 2 (chronic pain and/or instability) cannot be counted toward a diagnosis of hEDS in this situation.
3. Exclusion of alternative diagnoses that may also include joint hypermobility by means of hypotonia and/or connective tissue laxity. Alternative diagnoses and diagnostic categories include, but are not limited to, neuromuscular disorders (*e.g.* Bethlem myopathy), other hereditary disorders of the connective tissue (e.g. other types of EDS, Loeys-Dietz syndrome, Marfan syndrome), and skeletal dysplasias (*e.g.* osteogenesis imperfecta). Exclusion of these considerations may be based upon history, physical examination, and/or molecular genetic testing, as indicated.

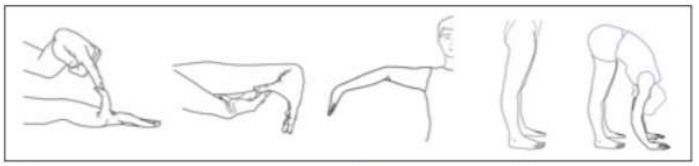
Criterion 1 – Generalized joint hypermobility

CRITERION 1 – Generalized Joint Hypermobility

One of the following selected:

- ☐ ≥6 pre-pubertal children and adolescents
- ☐ ≥5 pubertal men and woman to age 50
- ☐ ≥4 men and women over the age of 50

Beighton Score: _____/9



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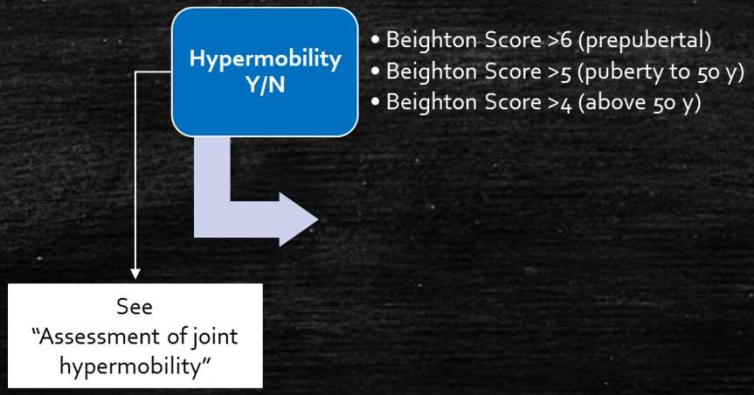

Criterion 2 –
Two or more features from A, B, C

Skin & tissue

Skeletal & teeth

Cardio-vascular

MILD

CRITERION 2 – Two or more of the following features (A, B, or C) must be present

Feature A (five must be present)

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- ☐ Bilateral piezogenic papules of the heel
- ☐ Recurrent or multiple abdominal hernia(s)
- ☐ Atrophic scarring involving at least two sites and without the formation of truly papyraceous and/or hemosideric scars as seen in classical EDS
- ☐ Pelvic floor, rectal, and/or uterine prolapse in children, men or nulliparous women without a history of morbid obesity or other known predisposing medical condition
- ☐ Dental crowding and high or narrow palate
- ☐ Arachnodactyly, as defined in one or more of the following: (i) positive wrist sign (Walker sign) on both sides, (ii) positive thumb sign (Steinberg sign) on both sides
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- ☐ Aortic root dilatation with Z-score >+2

Feature A total: _____/12

Feature B

- ☐ Positive family history; one or more first-degree relatives independently meeting the current criteria for hEDS

Feature C (must have at least one)

- ☐ Musculoskeletal pain in two or more limbs, recurring daily for at least 3 months
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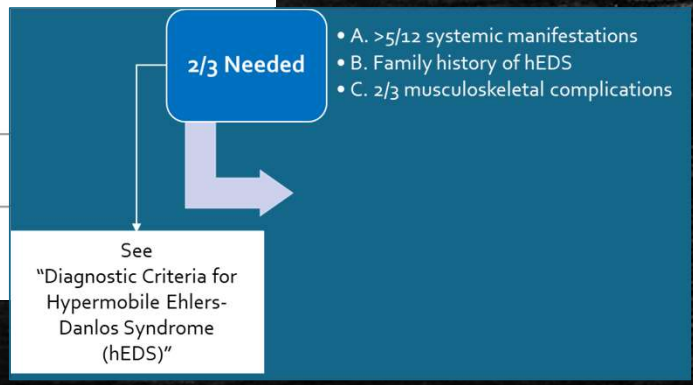
- ☐ Recurrent joint dislocations or frank joint instability, in the absence of trauma



Criterion 2 – Feature A skin examples

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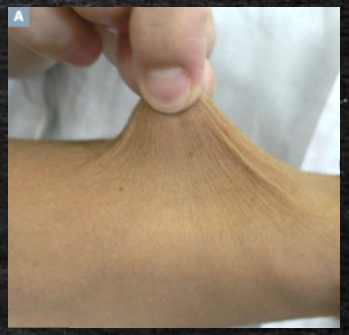
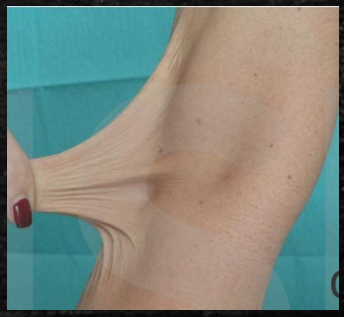
hEDS



Classic EDS



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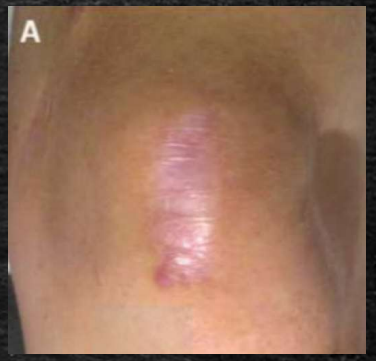
hEDS



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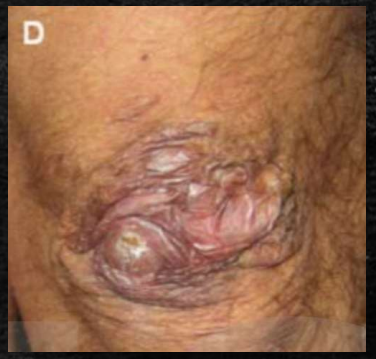

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Feature B

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Feature C (must have at least one)

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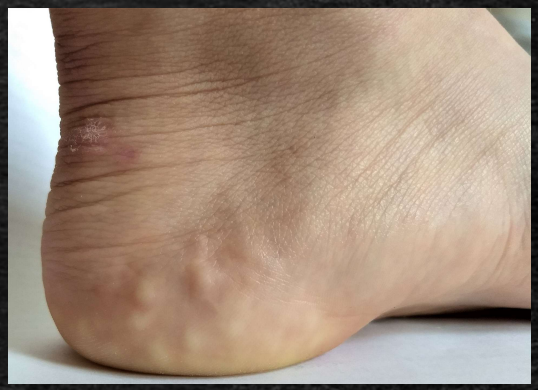
- ☐ Recurrent joint dislocations or frank joint instability, in the absence of trauma

Piezogenic papules



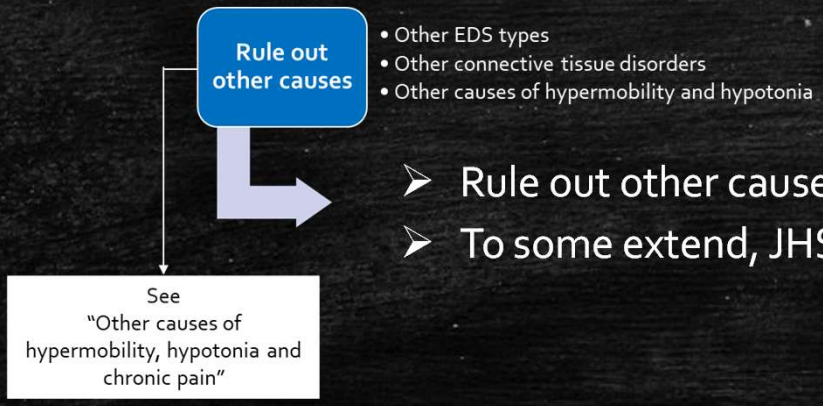
Common features in JHS/hEDS that are not diagnostic criteria

- A range of conditions can accompany hEDS, although there is not enough data for them to become diagnostic criteria.
- While they are associated with hEDS, they are not proven to be the result of hEDS and they are not specific enough to be criteria for diagnosis.
- Some of these include sleep disturbance, fatigue, postural orthostatic tachycardia, functional gastrointestinal disorders, dysautonomia, anxiety, and depression.
- These conditions may be more debilitating than the joint symptoms; they often impair daily life, and they should be considered and treated.
- Confusingly, there can be an association between autoimmune disorders and hEDS; therefore, a diagnosis of an autoimmune rheumatologic disorder may not completely exclude the diagnosis of a connective tissue disorder.

Criterion 3 –
ALL of the following must be met

CRITERION 3 – All of the following prerequisites MUST be met

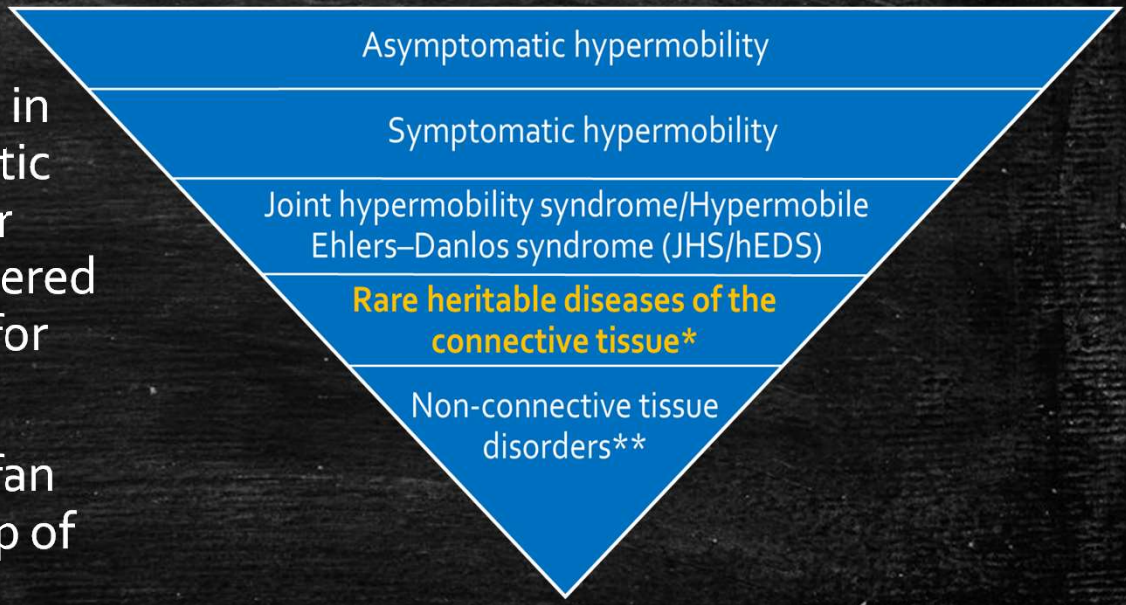
1. Absence of unusual skin fragility, which should prompt consideration of other types of EDS
2. Exclusion of other heritable and acquired connective tissue disorders, including autoimmune rheumatologic conditions. In patients with an acquired CTD (*e.g.* Lupus, Rheumatoid Arthritis, etc.), additional diagnosis of hEDS requires meeting both Features A and B of Criterion 2. Feature C of Criterion 2 (chronic pain and/or instability) cannot be counted toward a diagnosis of hEDS in this situation.
3. Exclusion of alternative diagnoses that may also include joint hypermobility by means of hypotonia and/or connective tissue laxity. Alternative diagnoses and diagnostic categories include, but are not limited to, neuromuscular disorders (*e.g.* Bethlem myopathy), other hereditary disorders of the connective tissue (e.g. other types of EDS, Loeys-Dietz syndrome, Marfan syndrome), and skeletal dysplasias (*e.g.* osteogenesis imperfecta). Exclusion of these considerations may be based upon history, physical examination, and/or molecular genetic testing, as indicated.



- Rule out other causes of hypermobility, hypotonia, and chronic pain
- To some extend, JHS/hEDS is an exclusion diagnosis

Recognizing conditions with increased risk of vascular complications

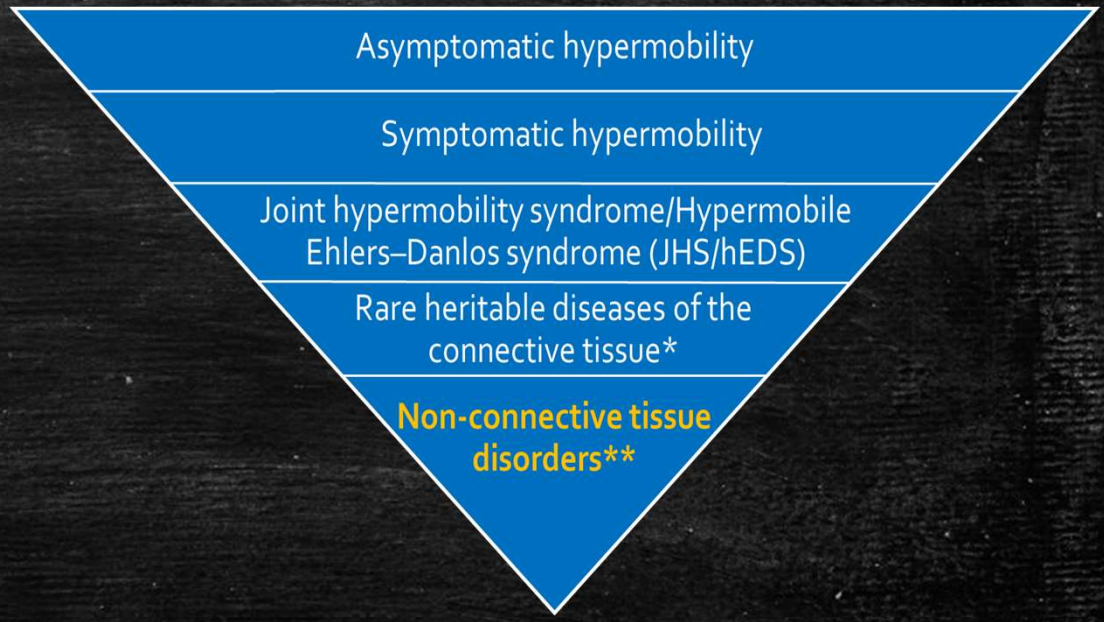
- Perhaps the most challenging in some cases is whether a genetic syndrome with risk of vascular complications must be considered which would prompt referral for consultation.
- Examples: vascular EDS, Marfan syndrome or the related group of Loeys-Dietz syndrome or homocystinuria



Non-connective tissue disorders with presentations that overlap with hEDS

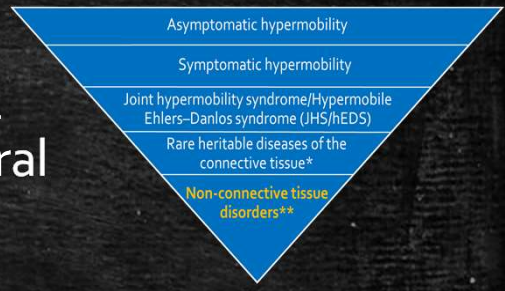
Generalized hypermobility can be a feature of several groups of disorders involving systems other than connective tissue:

- Neuromuscular and myopathic disorders
- Gastrointestinal disorders
- Allergy/Immunology
- Chronic pain and headache

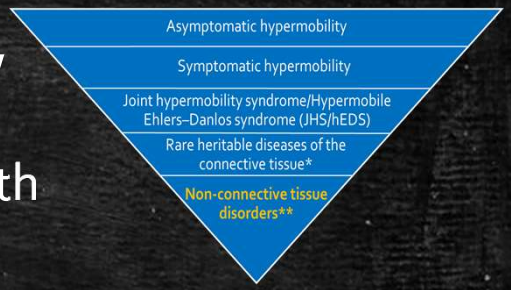


Primary myopathies may feature joint hypermobility and skin changes

- Examples: Collagen VI-related dystrophies and myopathies, Collagen XII related myopathy/EDS overlap syndrome, RYR1 and SEPN1 related myopathies, and Multiminicore and Central core disease.
- Congenital myopathies more often show distal rather than generalized hypermobility and are frequently accompanied by congenital hip dislocation (especially in COL6 and RYR1 related conditions).
- COL6 related dystrophies have prominent and progressive joint contractures, typically occurring in the shoulders, elbows, hips, knees, and Achilles tendons, but also in the finger flexors.
- Look for evidence of joint hypermobility as well as contractures in the hands and fingers.

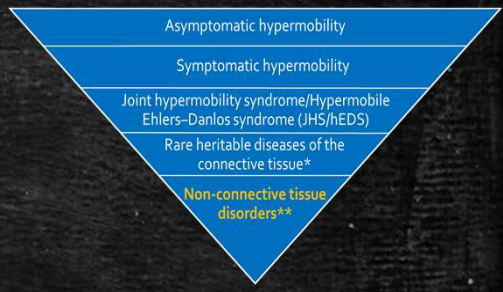


Functional GI disorders



- Functional GI disorders are common and may include GERD, delayed gastric emptying and irritable bowel syndrome.
- Fibromyalgia and chronic fatigue syndrome may present with overlapping GI symptoms.
- Celiac disease may coexist with EDS or be misdiagnosed as EDS.
- Common features may include pain, fatigue, functional gastrointestinal disorders, and cardiovascular autonomic dysfunction.
- In younger patients, chronic abdominal pain, feeding intolerance, poor growth, and severe constipation may be the presenting complaint and may warrant a pediatric gastrointestinal evaluation.
- Multiple food allergies leading to eosinophilic gastrointestinal disease is another common associated problem in pediatric patients.

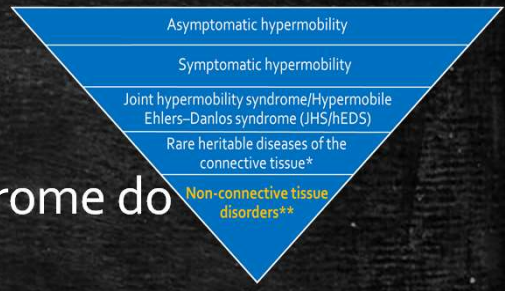
Allergy/Immunology



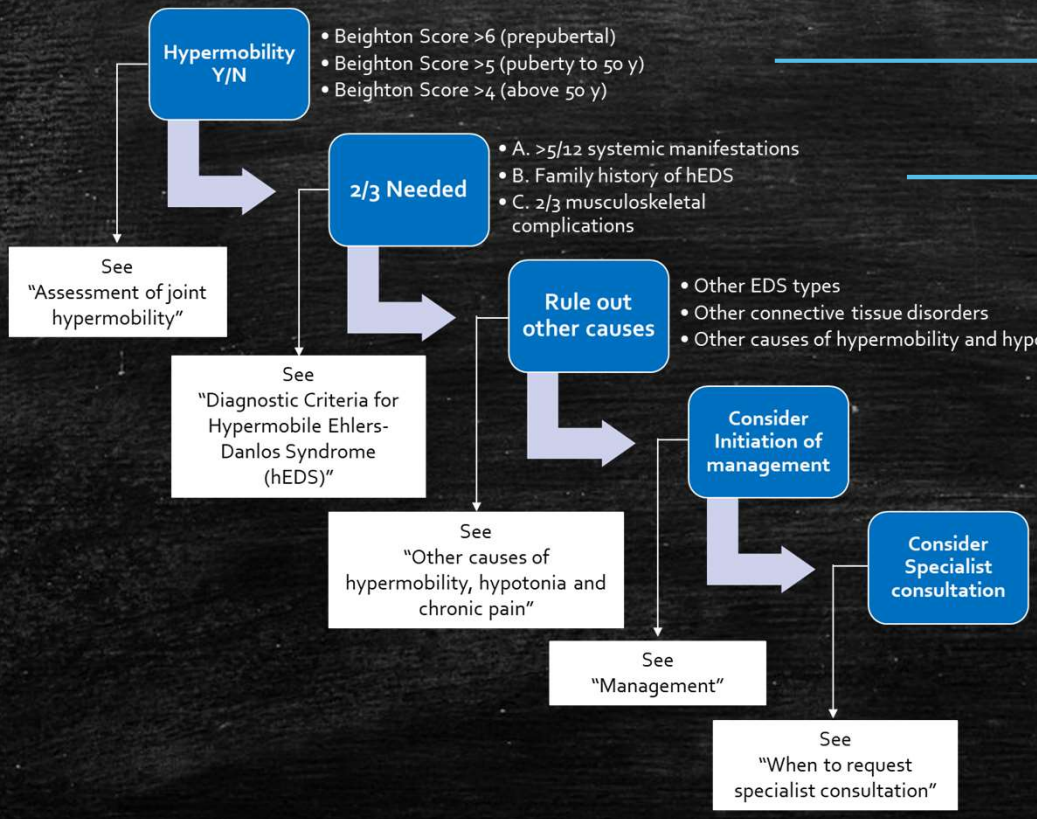
- Mast cell activation disorder is thought to be associated with some of the systemic symptoms in EDS.
- Laboratory tests such as serum tryptase levels and N-methyl histamine in urine are notoriously insensitive and should be ordered and interpreted by a specialist familiar with the condition.
- Differentiate from mastocytosis, which requires biopsy evidence.
- In addition to chronic hives and rashes, mast cell disease can also involve the GI tract as well as the bladder.

Chronic pain and headache

- Chronic pain is common in JHS/hEDS and there may be overlap with fibromyalgia and/or chronic fatigue syndrome.
- Most patients with fibromyalgia and/or chronic fatigue syndrome do not have JHS/hEDS.
- Chronic headaches including migraine and tension headaches are common in hEDS.
- Limited evidence suggests that Chiari I malformation and occipitoatlantoaxial instability may be more frequent, although the clinical relevance of this potential association is uncertain.
- Involvement of a neurologist specializing in headache management may be indicated.
- Referral for a formal pain team consultation may be warranted.



Algorithm for diagnosis, management and referral



Diagnostic Criteria for hEDS

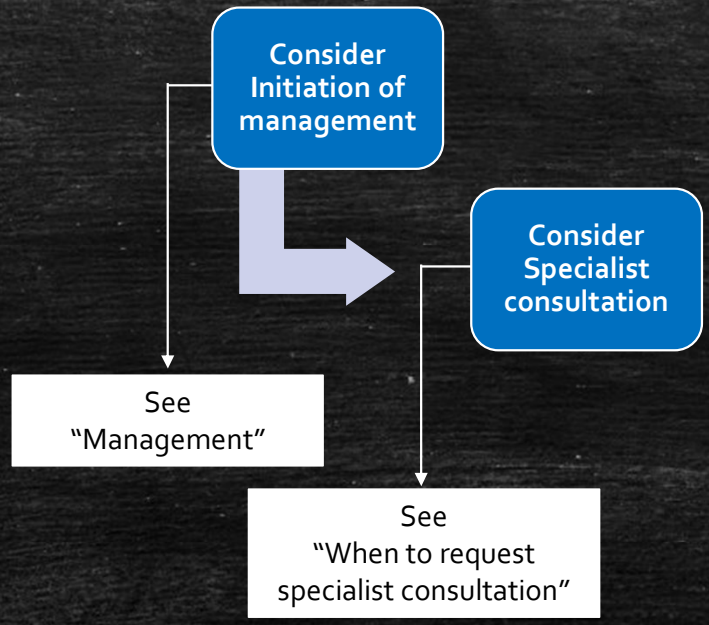
Criterion 1

Criterion 2

Criterion 3

Now that we established the diagnosis and excluded other causes, what's next?

Management and referral questions



Recommended evaluations and interventions

- Echocardiogram.
- Ophthalmology exam.
- Orthotics if the child has pes planus with ankle pronation.
- Physical therapy if the child has joint hypermobility, history of dislocations/subluxations, and/or joint pain.
- Occupational therapy for complaints of pain and fatigue in hands affecting handwriting or other activities of daily living.
- Modification of school program including a 504 plan.

Targeted evaluations and interventions

- GI consultation
- Urologic consultation
- Psychotherapy
- Multidisciplinary pain clinic
- Physiatry/physical medicine and rehabilitation
- Sleep evaluation
- Allergy/Immunology evaluation

POTS (postural orthostatic tachycardia syndrome)

- Many patients with joint hypermobility and EDS also have autonomic dysfunction altering the regulation of the involuntary nervous system that is made worse by decreased physical activity and overall physical deconditioning.
- Associated symptoms include dizziness, tachycardia, syncope, headache, nausea, digestive issues, foggy thinking, and anxiety.
- Orthostatic Vital Signs.
- Increase water intake and intake of salty snacks.
- Physical therapy (Levine protocol) https://www.dysautonomiainternational.org/pdf/CHOP_Modified_Dallas_POTS_Exercise_Program.pdf

When to request specialist consultation

- If the patient meets diagnostic criteria for JHS/hEDS and presents with mild to moderate symptoms, diagnosis and management can be through the primary care provider as outlined above.
- If the provider is not comfortable in assessing joint hypermobility using the Beighton scoring system a physical or occupational therapist may be helpful in performing this assessment and determining if the patient might benefit from therapy.
- If a patient presents with severe symptoms (e.g. multiple recurrent dislocations, severe skin manifestations, etc.), with or without additional features suggesting other causes of hypermobility, specialist consultation might be considered.

Guide for requesting specialist consultation

Hypermobility PLUS additional features suggesting possible	Consider consultation with
Genetic syndrome with increased risk of vascular complication	Medical Genetics
EDS other than JHS/hEDS	Medical Genetics
Chronic pain	Pain clinic and physical therapy
Non-connective tissue disorder	
• Neurologic/Neuromuscular	Neurology
• Gastrointestinal	Gastroenterology
• Autoimmune/Rheumatological	Rheumatology
• Allergy	Allergy/Immunology
• Functional Urologic disorders	Urology
• Structural heart defect and/or dysautonomia	Cardiology or Dysautonomia Specialist

Body system	Clinical features
Musculoskeletal	Severe generalized joint hypermobility with recurrent dislocation of multiple joints
	Progressive scoliosis or kyphoscoliosis in combination with joint hypermobility
	Chronic joint or muscle pain
Cutaneous	Hyperextensible and velvety soft texture skin beyond infancy
	Poor wound healing or extremely fragile skin
	Thin/translucent skin with prominent veins
	Bruising beyond what is expected in childhood
	Atrophic scarring ("cigarette paper-like scars")
Ophthalmological	Blue or grayish sclera beyond infancy
	Retinal fragility
	Severe myopia
	Lens subluxation/dislocation
Cardiovascular	Mitral Valve Prolapse (with or without regurgitation)
	Aortic Root Dilation
	Arterial tortuosity
	Arterial aneurysms
	Arterial dissections
Gastrointestinal	Intestinal rupture
	Severe constipation
	Feeding disorder with failure to thrive
	Rectal prolapse
	Severe dysphagia or motility dysfunction
Urological	Frequency, urgency (not associated with urinary tract infection)
	Enuresis
Gynecological	Uterine rupture
	Heavy menstrual bleeding
Family history	Confirmed diagnosis of EDS other than JHS/hEDS or another connective tissue disorder
	Family history of aneurysms or rupture of arteries or hollow organs (uterus, bowel)

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