

## **Hypermobile Ehlers-Danlos syndrome (hEDS) vs. Hypermobility Spectrum Disorders (HSD): What's the Difference?**

There has been a major revision in the approach to joint hypermobility (JH) as a whole. To recognize the continuum of JH, the hypermobility spectrum disorders (HSD) were created, ranging between, at one end, asymptomatic JH—someone who has no symptoms apart from their joints' capacity to move beyond normal limits—through to hypermobile EDS (hEDS), at the other end. The spectrum acknowledges that there can be severe effects on lives, whether they're the direct result of JH, or because they are known to be associated with having JH.

### **Hypermobile Ehlers-Danlos**

While hypermobile EDS (hEDS) remains the only EDS without a confirmed cause, the criteria for hEDS diagnosis have been tightened compared to the 1997 Villefranche nosology as determined by international consensus.

The essential difference between HSD and hEDS lies in the stricter criteria for hEDS compared to the HSD.

**If someone was diagnosed with hEDS before the 2017 criteria, there's no cause to seek a new diagnosis unless they decide to participate in new research or need to be reassessed for some other reason.**

### **HSD vs. hEDS: The New Diagnostic Criteria**

Treatment is more important than labels.

- Under the 2017 criteria, HSD or hEDS diagnosis, all other explanations for symptoms should be explored first, making sure they don't better fit another EDS subtype, injury, or another connective tissue disorder like Marfan.
- Symptoms and family history are then compared to the new criteria for hEDS (see table below).
- If they don't match the new criteria, physicians then look at the new criteria for HSD.
- Distinguishing the subtype of HSD relies on three factors:
  - Which joints are hypermobile;
  - the Beighton score;
  - the presence of other musculoskeletal involvements.

***What's important is: getting the proper diagnosis and treatment—not the label.***

2017 CRITERIA FOR HYPERMOBILE EDS	1997 CRITERIA FOR HYPERMOBILITY TYPE EDS
<p>The clinical diagnosis of hEDS requires the simultaneous presence of criteria 1 AND 2 AND 3.</p> <p><b>Criterion 1: Generalized joint hypermobility (GJH)</b>            • The Beighton score: <math>\geq 6</math> for pre-pubertal children and adolescents, <math>\geq 5</math> for pubertal men and women up to the age of 50, and <math>\geq 4</math> for those <math>&gt;50</math> years of age for hEDS.</p> <p>In individuals with acquired joint limitations (past surgery, wheelchair, amputations, <i>etc.</i>) affecting the Beighton score calculation, the assessment of GJH may include historical information using a five-point questionnaire; if the Beighton score is 1 point below the age- and sex-specific cut-off AND the 5PQ is 'positive' (= at least 2 positive items), then a diagnosis of GJH can be made. <b>[Notes and qualifications concerning this criterion in “The 2017 International Classification of the Ehlers-Danlos Syndromes,” Malfait <i>et al.</i>]</b></p> <p><b>Criterion 2: Two or more among the following features A, B and C MUST be present (for example: A and B; A and C; B and C; A and B and C)</b></p> <p><b>Feature A: systemic manifestations of a more generalized connective tissue disorder (a total of five must be present)</b></p> <ol style="list-style-type: none"> <li>1. Unusually soft or velvety skin</li> <li>2. Mild skin hyperextensibility</li> <li>3. Unexplained striae such as striae distensae or rubrae at the back, groins, thighs, breasts and/or abdomen in adolescents, men or prepubertal women without a history of significant gain or loss of body fat or weight</li> <li>4. Bilateral piezogenic papules of the heel</li> <li>5. Recurrent or multiple abdominal hernia(s) (<i>e.g.</i>, umbilical, inguinal, crural)</li> <li>6. Atrophic scarring involving at least two sites and without the formation of truly papyraceous and/or hemosideric scars as seen in classical EDS</li> <li>7. Pelvic floor, rectal, and/or uterine prolapse in children, men or nulliparous women without a history of morbid</li> </ol>	<p><i>Major criteria:</i></p> <ul style="list-style-type: none"> <li>• Skin involvement (hyperextensibility and/or smooth, velvety skin)</li> <li>• Generalized joint hypermobility</li> </ul> <p><i>Minor criteria:</i></p> <ul style="list-style-type: none"> <li>• Recurring joint dislocations</li> <li>• Chronic joint/limb pain</li> <li>• Positive family history</li> </ul> <p>The presence of one or both of the major criteria is necessary for clinical diagnosis; the presence of one or more minor criteria contributes to the diagnosis, but in the absence of a major criterion, they are not sufficient to establish a diagnosis.</p>

- obesity or other known predisposing medical condition
8. Dental crowding and high or narrow palate
  9. Arachnodactyly, as defined in one or more of the following:
    - a. positive wrist sign (Steinberg sign) on both sides;
    - b. positive thumb sign (Walker sign) on both sides
  10. Arm span-to-height  $\geq 1.05$
  11. Mitral valve prolapse (MVP) mild or greater based on strict echocardiographic criteria
  12. Aortic root dilatation with Z-score  $> +2$

***Feature B: positive family history, with one or more first degree relatives (biological mother, father, brother, sister) independently meeting the current diagnostic criteria for hEDS.***

***Feature C: musculoskeletal complications (must have at least one)***

1. Musculoskeletal pain in two or more limbs, recurring daily for at least 3 months
2. Chronic, widespread pain for  $\geq 3$  months
3. Recurrent joint dislocations or frank joint instability, in the absence of trauma (a or b)
  - a. Three or more atraumatic dislocations in the same joint or two or more atraumatic dislocations in two different joints occurring at different times
  - b. Medical confirmation of joint instability at 2 or more sites not related to trauma

***Criterion 3: all 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 connective tissue disorder (*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

towards 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.*, myopathic EDS, Bethlem myopathy), other hereditary disorders of connective tissue (*e.g.*, other types of EDS, Loeys-Dietz syndrome, Marfan syndrome), and skeletal dysplasias (*e.g.*, OI). Exclusion of these considerations may be based upon history, physical examination, and/or molecular genetic testing, as indicated.

**General Comment:**

- Many other features are described in hEDS but most are not sufficiently specific or sensitive to be included in formal diagnostic criteria, at the moment (see “Hypermobility Ehlers-Danlos Syndrome (a.k.a. Ehlers-Danlos Syndrome Type III and Ehlers-Danlos syndrome hypermobility type): Clinical Description, and Natural History” by Tinkle *et al.* [LINK]).
- These include but are not limited to: sleep disturbance, fatigue, postural orthostatic tachycardia, functional gastrointestinal disorders, dysautonomia, anxiety, and depression. These other systemic manifestations may be more debilitating than the joint symptoms, often impair functionality and quality of life, and should always be determined during clinical encounters.
- **While they are not part of the diagnostic criteria, the presence of such systemic manifestations may prompt consideration of hEDS in the differential diagnosis.**

<b>The Spectrum of Joint Hypermobility</b>			
<i>Type</i>	<i>Beighton score</i>	<i>Musculoskeletal involvement*</i>	<i>Notes</i>
Asymptomatic generalized JH	Positive	Absent	
Asymptomatic peripheral JH	Usually negative	Absent	JH typically limited to hands and/or feet
Asymptomatic localized JH	Negative	Absent	JH limited to single joints or body parts
Generalized-HSD	Positive	Present	
Peripheral-HSD	Usually negative	Present	JH typically limited to hands and/or feet
Localized-HSD	Negative	Present	JH limited to single joints or body parts
Historical-HSD	Negative	Present	Historical presence of JH
hEDS	Positive	Possible	
Musculoskeletal involvement includes trauma (micro- and macrotrauma), chronic pain, disturbed proprioception, and other traits (flat feet, misaligned bones in the elbow and big toe, mild-to-moderate scoliosis, kyphosis (outward curvature) of the upper spine, lordosis (inward curvature) of the lower spine).			

**Definition of terms:**

- Arachnodactyly: the fingers and toes are abnormally long and slender, in comparison to the palm of the hand and arch of the foot; and the individual's thumbs tend to also be pulled inwards towards the palm.
- hemosideric: yellowish-brown
- hypotonia: abnormally low muscle tone
- nulliparous: a woman who has never given birth
- piezogenic papules: small, painful, reversible herniations of underlying adipose tissue globules through the fascia into the dermis,
- papyraceous: thin or dry like paper; papery
- prolapse: a slipping forward or down of one of the parts or organs of the body
- striae distensae: stretch marks
- striae rubrae: red linear streaks