



Management and Referral Guide

Genetics

Hypermobile Ehlers-Danlos syndrome
Hypermobility Spectrum Disorders

Guidelines Referenced	<ol style="list-style-type: none"> 1 - https://onlinelibrary.wiley.com/doi/abs/10.1002/ajmg.c.31552 2 - https://onlinelibrary.wiley.com/doi/abs/10.1002/ajmg.c.31538 3 - https://onlinelibrary.wiley.com/doi/abs/10.1002/ajmg.c.31539 4 - https://ehlers-danlos.com/wp-content/uploads/hEDS-Dx-Criteria-checklist-1.pdf 5 - https://onlinelibrary.wiley.com/doi/abs/10.1002/ajmg.c.31545 6 - https://onlinelibrary.wiley.com/doi/abs/10.1002/ajmg.c.31554 7 - https://ehlers-danlos.com/wp-content/uploads/Educator-Parent-Guide-2016.pdf 8 - http://psycnet.apa.org/record/2014-04960-005
Background	<p>The Ehlers–Danlos syndromes (EDS) are a clinically and genetically heterogeneous group of heritable connective tissue disorders (HCTDs) characterized by joint hypermobility, skin hyperextensibility, and tissue fragility (1). The most common type of EDS is the hypermobile type (hEDS). Accurate prevalence estimation studies are lacking for hEDS, but this condition is likely the most common systemic inherited connective tissue disorder in humans which translates to approximately 2 million in the United Kingdom, 10 million in the United States, 17 million in Europe, and 255 million affected worldwide (2).</p> <p>A recent International EDS Consortium recognized 13 subtypes of EDS. For most of these subtypes, mutations have been identified in collagen-encoding genes, genes encoding collagen-modifying enzymes, and an array of novel genes. The definite diagnosis of all EDS subtypes, except for hEDS, relies on molecular confirmation with identification of (a) causative genetic variant(s).</p> <p>There is a clinical spectrum of joint hypermobility, ranging from asymptomatic symptoms, through “non-syndromic” hypermobility with secondary manifestations (Hypermobility Spectrum Disorders, HSDs), to hEDS (3). A diagnosis of hEDS is based on clinical features and should be assigned to those patients who meet the criteria (see below), which were revised in 2017 to allow for a better distinction from other joint hypermobility disorders.</p> <p>Many other features are described in hEDS, but most are not sufficiently specific nor sensitive at the moment to be included in formal diagnostic criteria. These include but are not limited to: sleep disturbance, fatigue, postural orthostatic tachycardia, functional gastrointestinal disorders, dysautonomia, anxiety, depression, and mast cell activation. These other systemic manifestations may be more debilitating than the joint symptoms, often impair functionality and quality of life, and should be evaluated for 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.</p>
Evaluation	<p>A printable checklist has been prepared to assist in reviewing the diagnostic criteria based on the history and physical examination (4). There is no specific genetic testing or other studies required to make a diagnosis of hEDS. The clinical diagnosis of hEDS needs the simultaneous presence of criteria 1, 2, and 3.</p> <p>Criterion 1: Generalized Joint Hypermobility (GJH)</p> <ul style="list-style-type: none"> • Beighton score - scoring system to delineate joint hypermobility: ≥ 6 for pre-pubertal children/adolescents, ≥ 5 for post-pubertal to 50 yo, and ≥ 4 for those > 50 yo

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1. 9 possible points
 - 1 point given if each of the first 4 maneuvers can be performed on a single extremity (i.e., 1 point if only 1 extremity involved, 2 points if both extremities involved). If possible, use of a goniometer is recommended for elbows and knees. Positive if >190 degrees of extension.
 - 1 point for forward bend, knees locked, and palms on the ground
2. <https://www.ehlers-danlos.com/assessing-joint-hypermobility/>
- 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:
 1. Can you now (or could you ever) place your hands flat on the floor without bending your knees?
 2. Can you now (or could you ever) bend your thumb to touch your forearm?
 3. As a child, did you amuse your friends by contorting your body into strange shapes or could you do the splits?
 4. As a child or teenager, did your shoulder or kneecap dislocate on more than one occasion?
 5. Do you consider yourself “double-jointed”?
- Criterion 2:** Two or More Among the Following Features (A, B, or C) Must Be Present
 - **Feature A:** systemic manifestations of a more generalized connective tissue disorder (a total of five must be present)
 1. Unusually soft or velvety skin
 2. Mild skin hyperextensibility
 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
 4. Bilateral piezogenic papules of the heel
 5. Recurrent or multiple abdominal hernia(s) (e.g., umbilical, inguinal, crural)
 6. Atrophic scarring involving at least two sites and without the formation of truly papyraceous and/or hemosideric scars as seen in classical EDS
 7. Pelvic floor, rectal, and/or uterine prolapse in children, men or nulliparous women without a history of morbid obesity or other known pre- disposing medical condition
 8. Dental crowding and high or narrow palate
 9. Arachnodactyly, as defined in one or more of the following: (i) positive wrist sign (Steinberg sign) on both sides; (ii) positive thumb sign (Walker sign) on both sides
 10. Arm span-to-height ≥ 1.05
 11. Mitral valve prolapse (MVP) mild or greater based on strict echocardiographic criteria
 12. Aortic root dilatation with Z-score ≥ 2



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	<ul style="list-style-type: none"> • Feature B: positive family history, with one or more first degree relatives independently meeting the current diagnostic criteria for hEDS. • Feature C: musculoskeletal complications (must have at least one): <ol style="list-style-type: none"> 1. Musculoskeletal pain in two or more limbs, recurring daily for at least 3 months 2. Chronic, widespread pain for ≥ 3 months 3. Recurrent joint dislocations or frank joint instability, in the absence of trauma <ul style="list-style-type: none"> ▪ ≥ 3 atraumatic dislocations in the same joint or ≥ 3 atraumatic dislocations in two different joints occurring at different times ▪ Medical confirmation of joint instability at two or more sites not related to trauma <p>Criterion 3: All the Following Prerequisites MUST Be Met</p> <ul style="list-style-type: none"> • Absence of unusual skin fragility, which should prompt consideration of other EDS types • 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. • 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.
Management Recommendations	<ul style="list-style-type: none"> • Referral to physical therapy for joint strengthening/stabilization; orthopedics evaluation as needed • Low-impact activities: swimming, biking, walking, golf, elliptical machine, rowing, etc • Medication: Ibuprofen/Tylenol as needed, additional pain medication • Magnesium (Epsom salt baths, transdermal oil/cream, oral) • Vitamin C (500mg-2g) can be used for bruising • Braces on various joint as needed (e.g., fingers, knees), arch support for flat feet (shoes, inserts); cushions • For symptoms of postural orthostatic tachycardia syndrome: increased water and salt intake, compression stockings, walking, cardiology evaluation as needed • For abdominal symptoms: small frequent meals, diets involving less inflammatory foods, trial of reducing dairy, gluten, sugars, etc; consider a referral to gastroenterology or nutritionist to ensure a healthy diet that minimally induces GI symptoms and inflammation • Antihistamines daily or as needed for hives • For school-aged children: modifications for school as needed (e.g., PE, increased time between classes, use of an elevator, etc)



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	<ul style="list-style-type: none"> • Optimize sleep quality • Consider cognitive behavioral therapy for pain management • Consider massage therapy/bodywork (acupuncture, etc), biofeedback, meditation/breathing exercises • Consider being involved with a local support group • Additional resources for patients and providers: <ul style="list-style-type: none"> ○ 'The Joint Hypermobility Handbook', by Brad Tinkle, MD, PhD ○ The EDS Society (www.ehlers-danlos.com) ○ GeneReviews on hEDS (https://www.ncbi.nlm.nih.gov/books/NBK1279/) ○ ECHO Project through the EDS Society (https://www.ehlers-danlos.com/echo/)
When to Refer	<p>Conditions for which your patient would benefit from a Medical Genetics consultation:</p> <ul style="list-style-type: none"> • EDS-vascular type: less significant joint hypermobility, thin/translucent skin, aneurysm or dissection of medium and large arteries, organ rupture (bowels, uterus, etc) • Marfan syndrome: hypermobility of hands/feet, a tall/thin build, aortic root dilation or dissection, lens dislocation