

**Hypermobility** is a general term that describes movement beyond a normal range of motion, sometimes leading to pain and systemic issues. Hypermobility is more common in females, younger individuals, and certain ethnic populations. Hypermobility is a spectrum of disorders, from benign asymptomatic flexibility to complex heritable connective tissue disorders like hypermobile Ehlers-Danlos Syndrome (hEDS). Collagen irregularities and mutations are thought to account for the wide spectrum of potential tissue changes. When collagen formation is altered, fibrils become thinner, less cross-linked, and more extensible, leading to ligamentous laxity and tissue fragility.

The 2017 nosology formally refers to the **2017 International Classification of the Ehlers-Danlos Syndromes (EDS)**. This revised classification system was a significant update to the previous 1998 Villefranche nosology.

- **Ehlers–Danlos syndromes (EDS):** a group of heritable connective tissue disorders; 14 genetically defined subtypes in the 2017 International EDS classification.<sup>1</sup> Most EDS subtypes have known molecular causes and confirmatory genetic testing; the exception is hypermobile EDS (hEDS), currently diagnosed clinically because a single genetic test is not available. The prevalence of all types of EDS affects an estimated 1 in 3000 to 1 in 5000 people.<sup>2</sup>
  - **Hypermobile EDS (hEDS):** the most common EDS subtype.
    - hEDS was formerly called Ehlers-Danlos syndrome, type III. It was considered an inherited autosomal dominant trait characterized by hypermobility of the joints with minimal abnormalities of the skin.
    - Research suggests dysregulated extracellular matrix (ECM) signaling rather than a single collagen gene defect is at play. Abnormalities in fibroblast mechanics, TGF-β signaling, and TNXB expression impact the adhesion of cells to collagen, tissue architecture, epithelial integrity, and the organization of collagen in the ECM.
- **Hypermobility Spectrum Disorders (HSD):** 2017 criteria established by the International Consortium on the Ehlers–Danlos Syndromes and Related Disorders characterize HSD as symptomatic joint hypermobility that does not meet full hEDS criteria and should be diagnosed clinically. The 2017 nosology formally separated HSD from hEDS to prevent overdiagnosis of hEDS. Clinical overlaps and many shared comorbidities (pain, autonomic symptoms, GI symptoms) are common.<sup>3, 4</sup>
- **Generalized joint hypermobility:** asymptomatic joint hypermobility that affects roughly 1–20% of the general population, depending on the criteria used.
  - Joint hypermobility syndrome (JHS) and benign joint hypermobility syndrome (BJHS)<sup>26</sup> are alternate names typically associated with hEDS and HSD.
  - BJHS: hypermobility in at least four joints without any concurrent medical condition according to *Pediatric Rheumatology*.

History	
<p>Patients with hypermobility commonly experience generalized joint laxity, which is frequently accompanied by joint pain, musculoskeletal complaints, and a predisposition to joint dislocations or subluxations.</p> <p>Pain linked to hypermobility may stem from various sources:</p> <ul style="list-style-type: none"> <li>• Genetic disorders, including Loeys-Dietz syndrome, Marfan syndrome, osteogenesis imperfecta, and Stickler syndrome.</li> <li>• Neuromuscular conditions such as cerebral palsy or muscular dystrophy.</li> <li>• Physical activity with repetitive movements in high-impact sports like gymnastics, dance, and cheerleading.</li> <li>• Postural irregularities</li> <li>• Trauma</li> </ul> <p>A comprehensive clinical assessment that includes detailed medical history, appropriate physical examination, and potential diagnostic testing is necessary to identify underlying causes.</p>	<p>Multiorgan symptoms are common in patients with various types of hypermobility, making the definitive diagnosis a prolonged process for the average patient; a recent study showed that it takes ~14 years to obtain a diagnosis.<sup>16</sup> A patient might:</p> <ul style="list-style-type: none"> <li>• Have long-standing multi-system complaints with normal imaging and lab results.</li> <li>• Have multiple “soft” diagnoses (IBS, fibromyalgia, chronic fatigue, anxiety, TMJ disorder).</li> <li>• Describe joint instability and easy bruising, unrelated to acute trauma.</li> <li>• Have a family history of similar symptoms, joint problems, or unexplained organ rupture.</li> <li>• Experience symptom exacerbation with prolonged standing, dehydration, or stress (suggesting autonomic involvement).</li> </ul>

Physical Examination Findings by Organ System	
<p><b>Autonomic / Cardiovascular</b><sup>21</sup></p> <ul style="list-style-type: none"> <li>• Dysautonomia (especially Postural Orthostatic Tachycardia Syndrome or POTS): orthostatic intolerance, palpitations, presyncope.</li> </ul> <p><b>Autonomic / Immune-like</b><sup>3</sup></p> <ul style="list-style-type: none"> <li>• Symptoms overlap with mast cell activation features (flushing, urticaria) in some patients.</li> </ul> <p><b>Gastrointestinal</b><sup>3, 6</sup></p> <ul style="list-style-type: none"> <li>• IBS-like symptoms, dyspepsia, constipation, dysmotility; GI symptoms are common and can be severe.</li> </ul> <p><b>Musculoskeletal / Integumentary</b><sup>3, 5</sup></p> <ul style="list-style-type: none"> <li>• Joint hypermobility, recurrent subluxations/ dislocations, tender joints, chronic regional pain, early osteoarthritis, soft/velvety skin, easy bruising, and widened scar formation.</li> </ul>	<p><b>Neurological/Neurocognitive</b><sup>3</sup></p> <ul style="list-style-type: none"> <li>• Proprioceptive deficits, coordination problems, “brain fog,” headaches, and small-fiber neuropathy.</li> </ul> <p><b>Ophthalmic</b><sup>24</sup></p> <ul style="list-style-type: none"> <li>• Convergence insufficiency, dry eyes, light sensitivity, myopia, and palpebral ptosis. Retinal detachment, choroidal neovascularization, glaucoma, and macular hole when high myopia is present (varies by subtype).</li> </ul> <p><b>Respiratory / ENT</b><sup>3</sup></p> <ul style="list-style-type: none"> <li>• Recurrent sinusitis, hoarseness, vocal cord issues, and diaphragmatic/respiratory muscle fatigue in some.</li> </ul>



## Ancillary Tests

### 5-Part (5PQ) Self-Report questionnaire <sup>10, 16</sup>

- Validated screening questionnaire: a useful adjunct if history of hypermobility is suspected. A “yes” to ≥2 items is a positive screen in many uses.

### Beighton Score (0–9) <sup>8, 9</sup>

- Quick objective screen for generalized joint hypermobility; age/sex cutoffs apply and score interpretation must consider lifespan. Widely used but has limitations as a sole test.

### Diagnostic Criteria for Hypermobile Ehlers-Danlos Syndrome (hEDS)<sup>23</sup>

- Published diagnostic checklist for doctors of all disciplines to diagnoses hEDS.

### Genetic Testing

- Available and recommended when clinical features suggest a monogenic EDS subtype (e.g., vascular EDS — *COL3A1*, classical EDS — *COL5A1/COL5A2*, etc.). Multi-gene NGS panels from clinical labs routinely test ~20+ genes for EDS subtypes; a negative test does **not** rule out hEDS. <sup>15</sup>

### Targeted Functional Tests <sup>14</sup>

- Strength, mid-range isometrics, proprioception testing, dynamic stability (single-leg squat, step-downs), and load-tolerance assessments. Use these to build rehabilitation plans.
- The Upper Limb Hypermobility Assessment Tool 25, the Lower Limb Assessment Scale (LLAS) and modified Beighton/line drawings 12, 13 for limb-specific and self-reported variants.

### Tilt Table Test – diagnoses conditions (like POTS) that cause dizziness, lightheadedness, or syncope

- Positive result. Blood pressure drops and heart rate changes, causing dizziness or fainting during the test.
- Negative result. Heart rate increases only slightly. Blood pressure doesn't drop significantly, and there are no symptoms of fainting.

## Treatment Options

### Autonomic (POTS) Management <sup>21, 22</sup>

- Non-pharmacologic (fluids, salt, compression garments, physical reconditioning).
- Pharmacologic (midodrine, fludrocortisone, beta-blockers, ivabradine depending on subtype and tolerability).
- Coordinate with cardiology/autonomic specialists.

### GI & other organ-specific care <sup>6, 7</sup>

- Manage the corresponding functional/ organic disorder (IBS/dysmotility) with appropriate gastroenterology referral; nutrition and motility treatments should be individualized.

### Pain management <sup>18, 19, 20</sup>

- Follow chronic pain guidelines: multimodal approach (education, graded activity, CBT when indicated, physical rehab).
- Pharmacologic agents (for neuropathic features) commonly used include gabapentin/pregabalin, SNRIs (duloxetine), and tricyclic antidepressants; evidence in hEDS is extrapolated from neuropathic/chronic pain literature rather than EDS-specific RCTs. Opioids are generally not a long-term solution.

### Procedural Interventions <sup>3</sup>

- Prolotherapy, injections, surgery: consider carefully — discuss higher risk of wound complications, poorer tissue quality, decreased responsiveness to anesthetics, and weigh functional benefit vs risk; collaborate with providers experienced with connective tissue disorders.

### Rehabilitation and Exercise <sup>14,17</sup>

- Graduated, hypermobility-aware programs (mid-range isometrics → controlled isotonic → proprioception & stability work) show consistent benefit in small trials and reviews and are a cornerstone of management.
- Avoid repetitive end-range and ballistic loading early in rehab.

### Potential ICD 10 Codes\*

- Q79.62** = Hypermobile Ehlers-Danlos syndrome
- Q79.61** = Classical Ehlers-Danlos syndrome
- Q79.63** = FibroVascular Ehlers-Danlos syndrome
- Q79.69** = Other Ehlers-Danlos syndromes
- Q79.60** = Ehlers-Danlos syndrome, unspecified
- M35.7 (Hypermobility Syndrome)** = Hypermobility spectrum disorder (HSD)\*\*
- M25.5** = Pain in joint (arthralgia), a 5th character can be added to specify the joint (M25.50–M25.59)

### DDX List for this Condition

- Autonomic dysregulation, including POTS
- Chronic fatigue syndrome
- Chronic regional pain syndrome
- Endocrine disorders such as hypothyroidism and Cushing’s syndrome
- Functional GI disorders such as irritable bowel syndrome (IBS) and dyspepsia
- Fibromyalgia
- Systemic Lupus Erythematosus (SLE)
- Mast Cell Activation Syndrome (MCAS)
- Myalgia/Myofascial pain syndrome
- Loeys–Dietz syndrome, Marfan syndrome, osteogenesis imperfecta, and Stickler syndrome also manifest with joint hypermobility and musculoskeletal pain due to mutations affecting collagen or proteins crucial in connective tissue synthesis and maintenance.

\*per the Ehlers-Danlos Society

\*\*HSD does not have an official code in any of the ICD-10 coding systems. Healthcare providers often use the code **M35.7 – hypermobility syndrome** for people with HSD. While this code technically refers to hypermobility syndrome, it is often used for HSD as a practical workaround. These codes were identified through consultation with experienced clinicians across various specialties and regions.

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