Genetics & Genomic Medicine Service
Brigham and Women's Hospital

We regret that due to a shortage of clinical providers and extremely limited resources, the BWH adult genetics clinic is unable to schedule patients for referral indications related to connective tissue disorders, joint hypermobility and/or Ehlers-Danlos syndrome (EDS), effective January 2022.

While we hope that our clinical program will be able to eventually resume clinical care for this patient population, we do not have an estimated timeframe for when this might happen. This letter is designed to help summarize clinical evaluation and management considerations specific to hypermobility type EDS (hEDS) to an attempt to support and optimize patient care.

Hypermobility EDS

Individuals with EDS have a defect in their connective tissue, which provides support to many parts of the body such as the skin, muscles, and ligaments. There are multiple subtypes of EDS that are associated with variable features and severity. Hypermobility EDS (hEDS) is characterized primarily by hypermobile joints and mildly hyperextensible skin. Musculoskeletal complications include susceptibility to subluxations and dislocations, often with no or minimal trauma, degenerative joint disease, and chronic pain. Skin may be soft, mildly hyperextensible, and bruise easily. Because connective tissue is found throughout the body, individuals with EDS can have a wide range of medical problems, such as functional bowel disorders and autonomic dysfunction.

Genetic Testing

Our genes are in every cell of our body and function as the instructions book for how our bodies are built and function. Our genes are spelled out by a series of letters (A, T, G, and C) that code for amino acids, which build the proteins that work in our bodies. Genetic disorders are caused by having one or more spelling changes (also called 'pathogenic variant', or 'mutation') in our genes that prevent the protein for that gene from being made properly. Different types of genetic disorders can be inherited in different ways. Most genetic disorders are caused by spelling changes that are passed on from one or both parents, though some spelling changes can occur brand new in someone and not be inherited from a parent.

Current genetic testing can provide three possible types of results- possible, negative, and a 'variant of uncertain clinical significance' (VUS). A positive result means that a genetic change was found that is known to cause or contribute to a specific genetic disorder. This type of result could confirm a diagnosis for an individual's medical history, clarify future disease risks, guide appropriate management or screening, inform reproductive risks and options, and facilitate targeted genetic testing for at-risk relatives. A negative result means that there were no genetic changes that are known to cause or contribute to disease- this type of result typically reduces, but does not completely eliminate, the likelihood of an underlying genetic disorder. Lastly, a VUS result indicates that a genetic change was found, but there is not enough information available to determine the meaning of the change (ie. if it can cause genetic disease or not).

Genetic testing may or may not be done to help clarify the likelihood of a diagnosis of hypermobility EDS. Negative genetic testing does not rule out a diagnosis of hEDS, but would reduce the likelihood of a diagnosis of a monogenic connective tissue disorder like vascular type EDS. Some genetic testing panels include genes associated with connective tissue disorders that confer an increased risk for aortopathy and vascular complications, such as the *COL3A1* gene, which is the gene associated with causing vascular type EDS.

Genetic testing for genes associated with different types of EDS and other connective tissue disorders can be ordered by providers and/or initiated by patients. Invitae Genetics is a specific lab that offers patient initiated testing (https://www.invitae.com/en/genetic-illness/how-testing-works). Our clinic providers consider Invitae to be a high quality and reputable medical genetics lab. BWH and our clinical genetics team do not have an affiliation or financial interest with Invitae.

Diagnosing hEDS

While some subtypes of EDS are known to be caused by one or more mutations in a specific gene, hypermobility type EDS (which is the most common type of EDS) does not have a well-established genetic cause. For this reason, hEDS is not diagnosed through positive genetic testing. Instead, hEDS is diagnosed clinically based on physical exam findings, medical history, and family history.

An international body of experts spent several years reviewing diagnosis and treatment of hypermobility type EDS and put together a publication summarizing their primary findings[1]. One of their conclusions was that hypermobility type EDS can be diagnosed by non-geneticists and does not require genetic testing for confirmation. While some patients are diagnosed with hEDS in a medical genetics clinic setting, the diagnosis can be made by non-geneticists (physicians, nurses, and physicians assistants) based on specific clinical criteria and physical exam findings. This may be a more effective means of diagnosis for some individuals, given that geneticists do not typically treat or manage disease symptoms and the wait-time for an appointment with a geneticist typically exceeds that of other physician or clinical provider types.

Clinical Management of Hypermobility EDS

Individuals with hypermobile EDS can have a variety of additional medical problems. **The management of hypermobile type EDS should involve particular attention to the following:**

- **Joint protection** — It is important to "preserve and protect" joint function, with the goal of preventing recurrent joint dislocations, chronic joint pain, and early onset of osteoarthritis. Patients with joint pain and instability should be referred for physical therapy evaluation and management. Physical therapy should focus on low-impact, low-resistance exercise for strengthening of core and extremity muscles and joint stability. Joint hyperextension must be avoided. Recommended physical activities include swimming, elliptical machines, and walking.

[1] Bloom, L., Byers, P., Francomano, C., Tinkle, B., Malfait, F., & Steering Committee of The International Consortium on the Ehlers-Danlos Syndromes. (2017, March). The international consortium on the Ehlers–Danlos syndromes. In *American Journal of Medical Genetics Part C: Seminars in Medical Genetics* (Vol. 175, No. 1, pp. 5-7).

Contact sports and repetitive activities (such as running and weightlifting) should be avoided. Assistive devices may be used to improve joint stability.

- **Bone health –** Decreased bone density is common. This should be evaluated and monitored by DEXA scan, and bone density maximized through supplementation with calcium, vitamin D, and low-impact weight-bearing exercise.
- **Pain management** – Pain may include muscular or myofascial pain near the joints, neuropathic pain, osteoarthritic pain, temporomandibular dysfunction, and migraines. Preventive strategies and non-opioid pain management are important in the treatment and management of musculoskeletal pain. Patients with refractory pain may require referral for further evaluation in a pain clinic.
- **Cardiovascular** – Patients with hypermobile EDS should undergo evaluation for cardiovascular involvement, such as mitral valve prolapse and aortic dilation. There are no standardized protocols for such evaluation and monitoring in EDS, but it is generally recommended to obtain baseline screening echocardiography at least once in adulthood.
- **Autonomic dysfunction –** Postural orthostatic tachycardia syndrome (POTS) manifests as an excessive increase in heart rate and significant reduction in blood pressure on standing. Symptoms may include atypical chest pain, palpitations, and syncope or near syncope.
- **Gastrointestinal symptoms** – Functional bowel disorders are common, including gastroesophageal reflux, gastritis, delayed gastric emptying, and irritable bowel syndrome. It may be helpful for patients to see a gastroenterologist to help manage these symptoms.
- **Bleeding** – Mildly prolonged bleeding, epistaxis, bleeding from the gums (especially after dental extraction) and heavy periods may occur.
- **Pregnancy management** – Joint laxity and pain may increase through the course of the pregnancy. Labor and delivery may proceed more rapidly than usual.
- **Psychosocial support** — Individuals with hypermobility type EDS are at increased risk to be affected by depression, anxiety, fatigue, and sleep disturbance. Psychological counseling may be beneficial. In addition, cognitive behavioral therapy may help to manage chronic pain.
- **Surgery and other procedures** – In general, orthopedic surgery should be delayed in favor of non-invasive treatments, such as physical therapy and bracing. Individuals with hypermobile EDS are generally not susceptible to the wound healing complications that are associated with other types of EDS, but additional precautions (such as leaving stitches in longer than normal) may be considered.

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