Please find below the current version of the decline letter provided by Maritime Medical Genetics Service (MMGS) for patients referred to query hypermobile Ehlers-Danlos Syndrome or Hypermobility Spectrum Disorder. It is being made available to patients, physicians/clinicians and other allied healthcare professionals in the hopes that it will provide clear, concise guidance on how to diagnose and manage hEDS/HSD. This document also provides guidance for the management of common co-morbidities, information on possible co-morbidities, resources and further reading, and red flags that would necessitate a re-referral. Timely diagnosis and management is key to positive patient outcomes.

PLEASE NOTE: Carefully review information for differential diagnosis marked with a red exclamation, with close attention to criteria for referral or re-referral.

To: ____XXXXXXXXXXX_____

Fax: ___XXXXXXXXXXX____

Maritime Medical Genetics Service Phone: 902-470-8754 Fax: 902-470-8709

Regarding Patient: _____XXXXXXXXXXXXXXXXXXXXXXX_____

Joint hypermobility is a common finding in the general population. While we would like to still be able to offer a genetic appointment to all patients in our catchment area with a suspected diagnosis of hypermobile Ehlers-Danlos syndrome (hEDS), our wait list has unfortunately become unmanageable. **We are therefore returning this referral to you** with general advice that has been helpful to other patients with joint hypermobility.

The differential diagnosis for hypermobile EDS includes, in addition to primary rheumatologic conditions, a number of heritable connective tissue disorders. Some of these can be associated with thoracic aneurysms, which is why it is important for you to ensure that your patient does not have a family history of aneurysm, vascular dissection of hollow organ rupture.

- ! If your patient's echocardiogram shows an aortic dilatation, a mitral valve prolapse or a bicuspid aortic valve, please refer them back and include a copy of the echocardiogram with your referral.
- ! If your patient has a thoracic or brain aneurysm, a history of vascular dissection or of hollow organ rupture, please also refer them back indicating this history on the referral.
- ! If your patient has a positive family history of a first degree relative ONLY with thoracic or brain aneurysm, vascular dissection or hollow organ rupture, please refer them back, specifying this history on the referral.
- ! If your patient's relatives were diagnosed with another subtype of EDS other than hypermobile EDS, please refer your patient back and indicate this history on the referral.
- ! Finally, if your patient displays any of the following, please refer them back and indicate this history on the referral:
    - Very translucent skin
    - Atrophic scars
    - Very wide-spaced eyes (hypertelorism)
    - A bifid uvula
    - Extremely large bruises with minimal trauma
    - Pneumothorax
    - Atraumatic tendon ruptures

Thank you for helping us ensure that we are seeing the patients most likely to benefit from a Genetics clinic appointment in a timely manner. If your patient meets any of the criteria above, we would be happy to see them with a new referral.

For **pediatric** patients, we only accept referrals from a pediatrician. If your patient is in the pediatric age group, please refer to a pediatrician for initial assessments.

Lastly, the Atlantic EDS Society may be a good resource for your patient: www.atlanticedssociety.ca.

Please do not hesitate to contact us at the number above if you have any questions or concerns.

MANAGEMENT:

Joint hypermobility is a common finding in the general population. Approximately 5-10% of adults have generalized joint hypermobility which varies with age and ethnicity. Most hypermobile individuals do not experience complications.

In addition to joint hypermobility, individuals with hEDS and Hypermobility Spectrum Disorder (HSD) experience additional symptoms. The management of HSD and hEDS is the same. The core features of hEDS are generalized joint hypermobility, skin stretchiness and weakened connective tissues.

The current EDS classification describes 13 types. Most of these types are rare. The classical type, associated with very flexible joints and stretchy, fragile skin is estimated to affect 1 in 20,000 individuals. The vascular type, associated with flexible fingers, extremely thin skin and fragility of arteries and internal organs is estimated to affect 1 in 50,000. The other 10 types of EDS, usually associated with severe scoliosis and extreme joint laxity are very rare with a small number of patients described worldwide.

hEDS is the most common type, associated with joint subluxations, dislocations, soft tissue injuries, fatigue, dysautonomia and pain. The genetic cause(s) for it remain largely unknown. The recent classification of EDS (Malfait et al. 2017 PMID: 28306229) describe strict criteria for a diagnosis of hEDS. This is a clinical diagnosis based on an assessment of the degree and history of joint hypermobility, other physical features such as skin texture and scars, family history, typical symptoms of joint pain and the exclusion of an inflammatory arthritis or other hereditary diagnoses. These criteria are based on expert opinion and have yet to be validated.

HSD describes patients who have a degree of joint hypermobility, some other physical signs and symptoms, but do not technically meet these new criteria. It is important to note that patients with HSD and hEDS can be equally symptomatic with pain, fatigue, irritable bowel syndrome, dysautonomia and other symptoms. These symptoms are more common in patients with HSD and hEDS, compared to the general population.

We hope that the guidance below will help you and your doctors manage these symptoms.

Joint dislocations & subluxations:
Many patients with HSD/hEDS have repeated joint dislocations and subluxations (partial dislocation of a joint). These can occur spontaneously or with minor injury. The mainstay of management is physiotherapy (PT) aimed at muscle strengthening. HSD/hEDS patients experience ligament and tendon stretchiness, and joint pain, hence PT may need to be offered for a longer period than is usual. A focus on core strength and preventive management with pacing of activities can be very helpful. Surgical management may be helpful for some patients, although there is likely to be an increased risk of short term operative complications and relapse of instability for some patients. Chronic shoulder and patellar (knee cap) instability can be particularly troublesome to manage; aggressive rehabilitation and PT is recommended along with a surgical opinion if required.

There is no clear evidence that any particularly type of PT or activity is better than another; every individual patient will have a different pattern of joint hypermobility and symptomatology. Anecdotally non-weight bearing activities like swimming and cycling, muscle strengthening with Pilates, strengthening, movement based therapies like Tai Chi or Qi Gong may be helpful for both muscle strengthening and pain management. A list of management strategy resources for you and your doctor is at the end of this letter. This includes the Muldowney protocol, a specific PT program for hEDS patients.

Pain:
HSD/hEDS patients may experience joint pain, which can be difficult to manage, and some (but not all) progress to experience chronic pain. This may include complex pain disorders, symptoms suggestive of peripheral and central pain sensitization. Recovery times from injuries may be prolonged and patients

may need extended rehabilitation. Simple analgesia, (eg. acetaminophen/Tylenol) may be helpful. Opiate analgesia (Codeine, Percocet, Oxycodone, Hydromorphone, others) seems to be ineffective. A variety of different pain management strategies may be helpful, including cognitive behavioural therapies and mindfulness based therapies, specialized medication and advice from a pain specialist clinic is recommended. Anecdotally some patients report reduced response to local anesthetics (lidocaine).Careful anesthetic technique and maximizing dosage will help to improve the response to anesthetic. Headache is particularly prevalent in patients with HSD/hEDS, thorough assessment by your family doctor with a focus on musculoskeletal causes in the head, neck and jaw is recommended.

It is important to rule out inflammatory arthritis or osteoarthritis.

Skin Care:
HSD/hEDS patients may have a mild degree of skin involvement with prolonged wound healing. There is no one recommendation that fits all patients with regard to suture type, glue or other wound care. Health care providers should be aware of any history of skin healing problems, particularly in the emergency room. Some patients with HSD/hEDS have more significant wound healing problems with atrophic scars, require sutures to be applied generously in multiple layers, without tension and these to be left in for a longer (up to twice as long) period than average to assist with wound healing.

Bleeding and Bruising:
HSD/hEDS patients often experience a mild degree of easy bruising, which may occur with minor trauma. Severe bleeding requiring blood transfusion or re-admission to the operating theatre, bleeding into a large joint should prompt referral to a hematologist for further investigations for an alternative (blood/clotting related) cause.

Osteoarthritis (OA):
It is possible that HSD/ hEDS predisposes to the development of OA later in life for some patients. We know that mechanically unstable joints are one of the risk factors for OA. The genetic basis and other risks for OA are complex. Every person's risk will be different. Maintaining as active a lifestyle as possible and maintaining a healthy weight will minimize this risk.

Osteoporosis:
People with HSD/hEDS may be at an increased risk of having lower bone mineral density than the general population. Whether this results in increased rates of fracture is unknown. Adequate dietary calcium and vitamin D supplements are recommended. We a baseline bone density scan in early adulthood or earlier if there are unexplained (low trauma) fracture. Osteoporosis screening should be ongoing later life. (https://osteoporosis.ca/wp-content/uploads/Quick_Reference_Guide_October_2010.pdf).

Cardiovascular:
Mild (non-progressive) widening of the aorta has also been described in a minority of patients. Based upon the available studies, it appears that the majority of people with HSD/hEDS do not develop significant aortic dilation. We would recommend a baseline cardiology evaluation with imaging. Ongoing follow-up plan can be determined by the cardiologist.

Dysautonomia:
HSD/hEDS patients are more prone to postural symptoms of dizziness, neural mediated hypotention, postural orthostatic tachycardia syndrome (POTS). Patients with HSD/hEDS may have arrhythmia unrelated to EDS, which may need different management, referral for a cardiology assessment is recommended.

Bowel Function:
HSD/hEDS patients are at risk for functional bowel disorders/irritable bowel syndrome. The management for these symptoms is similar as for the general population. It is important that other causes for bowel dysfunction, (inflammatory bowel disease, celiac disease, polyps/bowel cancer) are assessed.

Psychological Impact:
Many HSD/hEDS patients encounter distress, anxiety, mood disorders which may be exacerbated by chronic pain and poor mobility. Cognitive Behavioural Therapies, Mindfulness and other psychological supports are recommended.

Obstetrics & Gynecology:
Women with HSD/hEDS may have an increased chance for premature rupture of the membranes and/or rapid labour (less than 4 hours). There are risks of poor wound healing following episiotomy repair. There is only a small amount of available medical literature examining these risks.

HSD/hEDS patients may be at an increased risk for pelvic organ prolapse both before and after childbirth. Kegel exercises during pregnancy are strongly recommended along with referral to gynaecology when required. HSD/hEDS patient surveys report painful sexual intercourse (dyspareunia) as a common finding.

Oral/Dentistry:
HSD/hEDS patients may have an increased risk of dental crowding, poor enamel, periodontal disease, gingivitis, gum recession and gum fragility. Regular checkups by a dentist are recommended. Temporomandibular joint (TMJ) dysfunction is common in hypermobile individuals, and may present with jaw pain and headache. This can be assessed by dentistry or family medicine.

Inheritance:
HSD/ hEDS most often follows an autosomal dominant pattern of inheritance with highly variable expression/penetrance. This means individual members of the same family who carry the HSD/hEDS faulty gene can have greatly varying degree of symptoms. For a person who has HSD/hEDS each of their children would have a 50% chance of inheriting the faulty gene and hence be at risk of developing HSD/hEDS and a 50% chance of not inheriting this condition. Unfortunately, the genes that can lead to HSD/hEDS, are not well understood at this time, therefore genetic testing is not possible. Diagnosis is based upon a physical examination and family history.

Possible Associations:

Research into HSD/hEDS continues to move forward. Some studies have suggested the following links:

1. Mast Cell Activation Syndrome (MCAS). This is a poorly understood (and somewhat controversial) condition; patients may develop sensitivity of one of the components of the bone marrow and connective tissue (mast cells). These cells release histamine as a normal response to external stimuli/injury/infection. Patients with MCAS have inappropriate mast cell activity which may result in episodes of hives, flushing, dizziness and GI dysfunction. Referral to an allergist is recommended.

2. Craniocervical syndrome. A rare cause of headache is spinal cord compression at the base of the skull. This results in unusual types of headache, and can affect the cranial nerves and spinal cord. Some experts believe that laxity of the ligaments of the neck may contribute to this very complex problem. Headache is very common and multifactorial in HSD/hEDS patients (>75% in some series), and routine care for headache management should include a neurological assessment with onward referral to neurosurgery where appropriate.

Medical Resources:

- Diagnostic Criteria: “The 2017 international classification of the Ehlers-Danlos syndromes.” Malfait F.et al., Am J Med Genet C Semin Med Genet. 2017, **PMID: 28306229**
- Adult Management: “Hypermobile Ehlers-Danlos Syndrome”, Genereviews, Levy H https://www.ncbi.nlm.nih.gov/books/NBK1279/
- Adult Physiotherapy: https://www.ehlers-danlos.org/information/physical-therapy-for-hypermobility/

- Muldowney protocol: https://www.muldowneypt.com/ehlers-danlos-syndrome-information/
- Management in Children: Evidence-Based Care Guideline for Management of Pediatric Joint Hypermobility Guideline 43, Cincinnati Children's Hospital, Brad Tinkle (PDF available online).
- Physiotherapy in Children: The evidence-based rationale for physical therapy treatment of children, adolescents, and adults diagnosed with joint hypermobility syndrome/hypermobile Ehlers Danlos syndrome Am J Med Genet C Semin Med Genet. 2017 **PMID: 28306230**

Websites and Support Groups for EDS:

- (Local) Atlantic Ehlers-Danlos Support: https://www.atlanticedssociety.ca
- Ehlers-Danlos Society: https://www.ehlers-danlos.com/
- Ehlers-Danlos Support (UK): https://www.ehlers-danlos.org/
- Hypermobility Syndromes Association: http://hypermobility.org/
- Genetics Research: A large donation has enabled a research study to be launched buy EDS International to try to identify the genetics basis for hEDS. You can register your interest and find further details at: at https://www.ehlers-danlos.com/eds-global-registry/

The International Consortium on Ehlers-Danlos Syndromes & Related Disorders
In Association with The Ehlers-Danlos Society

Diagnostic Criteria for Hypermobile Ehlers-Danlos Syndrome (hEDS)

This diagnostic checklist is for doctors across all disciplines to be able to diagnose EDS

Distributed by The Ehlers Danlos Society

Patient name: _____ DOB: _____ DOV: _____ Evaluator: _____

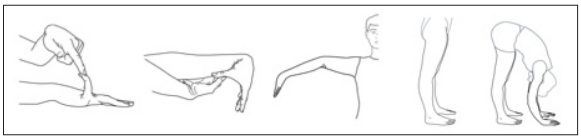
The clinical diagnosis of hypermobile EDS needs the simultaneous presence of all criteria, 1 ***and*** 2 ***and*** 3.

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 follow 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.

Diagnosis: _____