# Ehlers-Danlos Syndromes & Hypermobility Spectrum Disorders

## A Brief Clinical Overview

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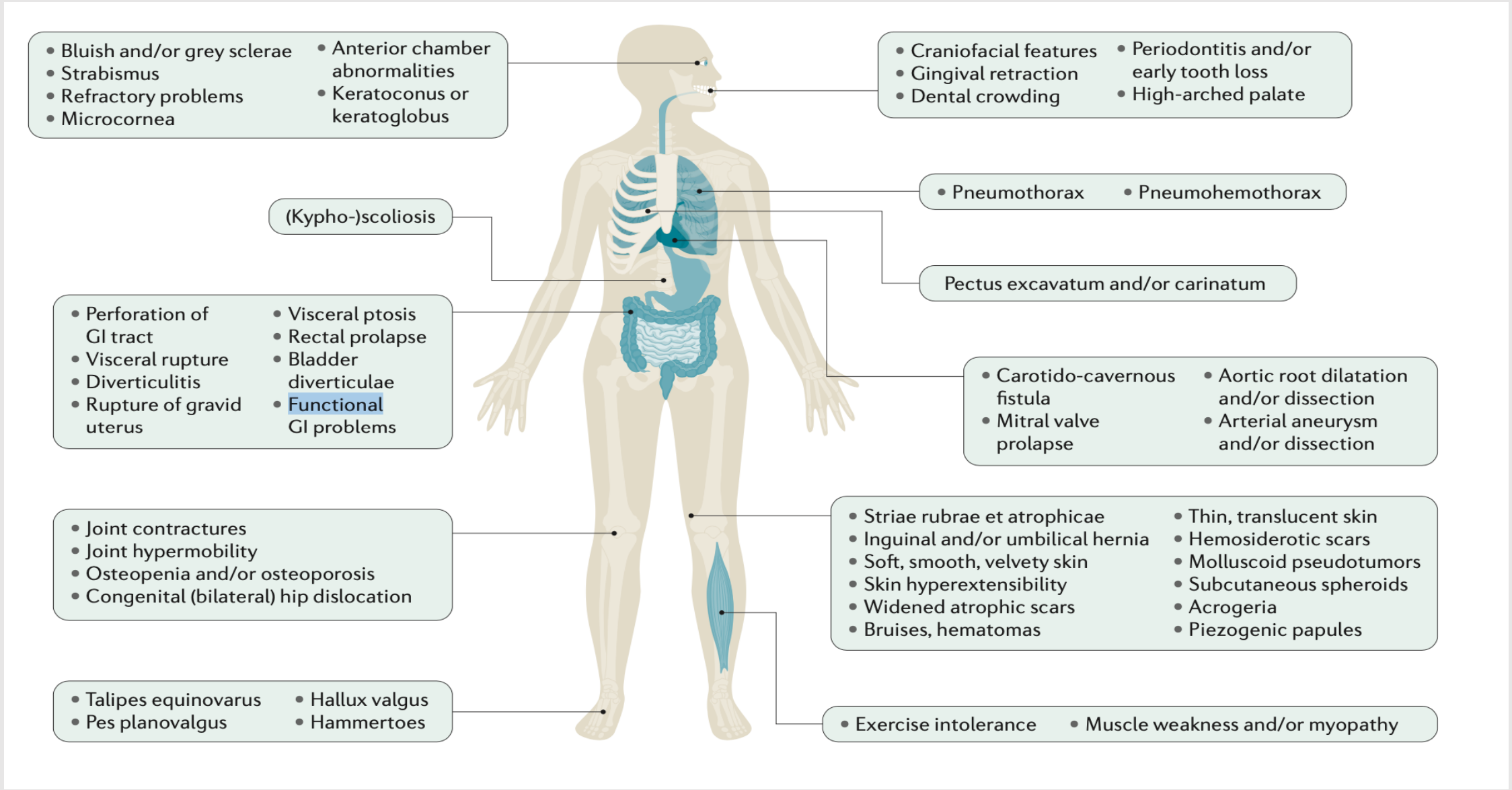
# Content

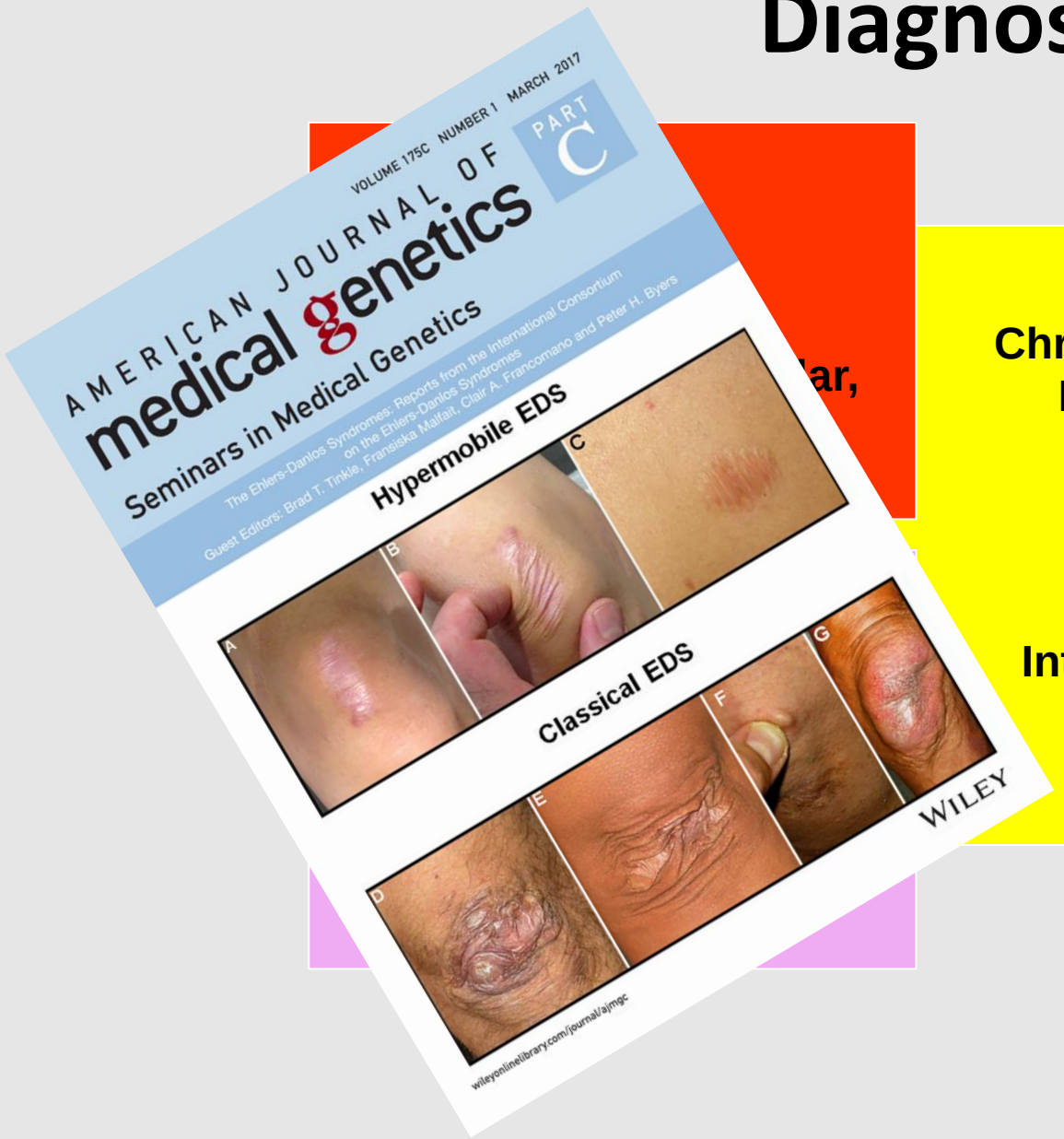
- What constitutes the Ehlers-Danlos Syndromes from a Diagnostic Criteria Perspective
  - Clinical Signs
  - Genetic Variants
- Comparing hEDS with Hypermobility Spectrum Disorder
- Am J Med Gen Part C March 2017

# Connective tissue is everywhere – EDS is a group of multisystemic disorders




Malfait F *et al* Nat Rev Dis Primers, 2020

# Many Related Concerns Not in the Diagnostic Criteria

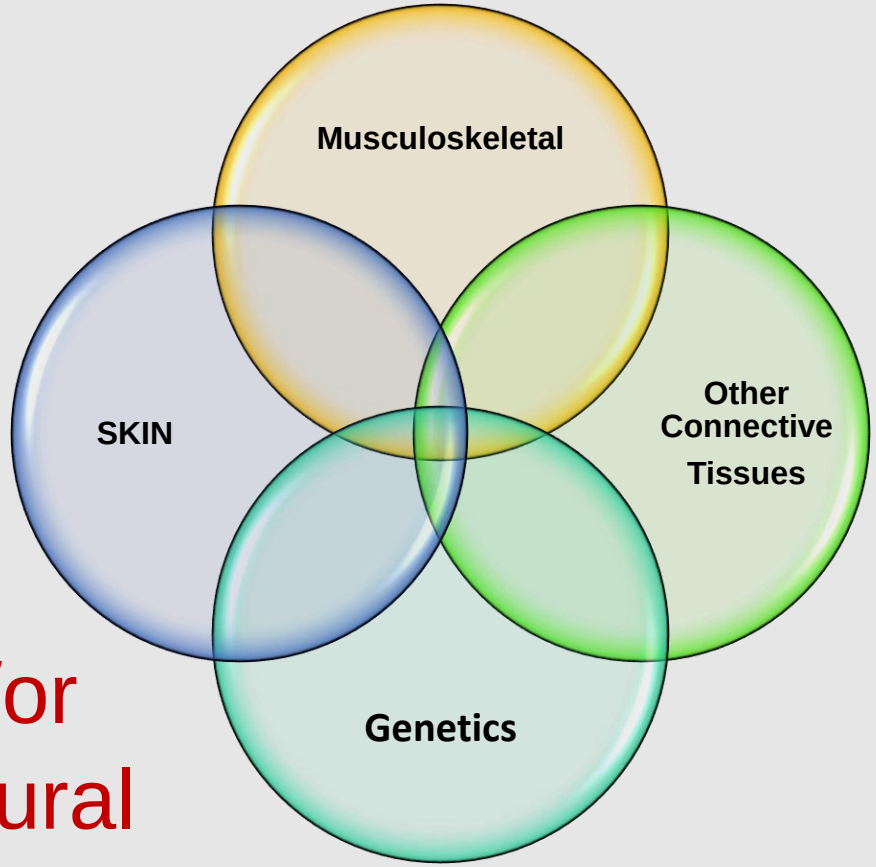



**Chronic Fatigue: Physical & Cognitive**

**Allergy Intoleran MC**

# What constitutes the Ehlers-Danlos Syndromes?

- Musculoskeletal pathology
- Skin complications
- Other structural tissue fragility
- For all but hEDS – identifiable genetic variation causing changes in production and/or function of collagen & related structural proteins



# hEDS Diagnostic Checklist

- Hypermobility
- Skin, Other Tissues, Body shape
- Family history of hEDS
- Pain and Joint Instability
- Exclusions / Other diagnoses

The International Consortium on Ehlers-Danlos Syndromes & Related Disorders

**Diagnostic Criteria for Hypermobile Ehlers-Danlos Syndrome (hEDS)**

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

Co-hosted 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)*

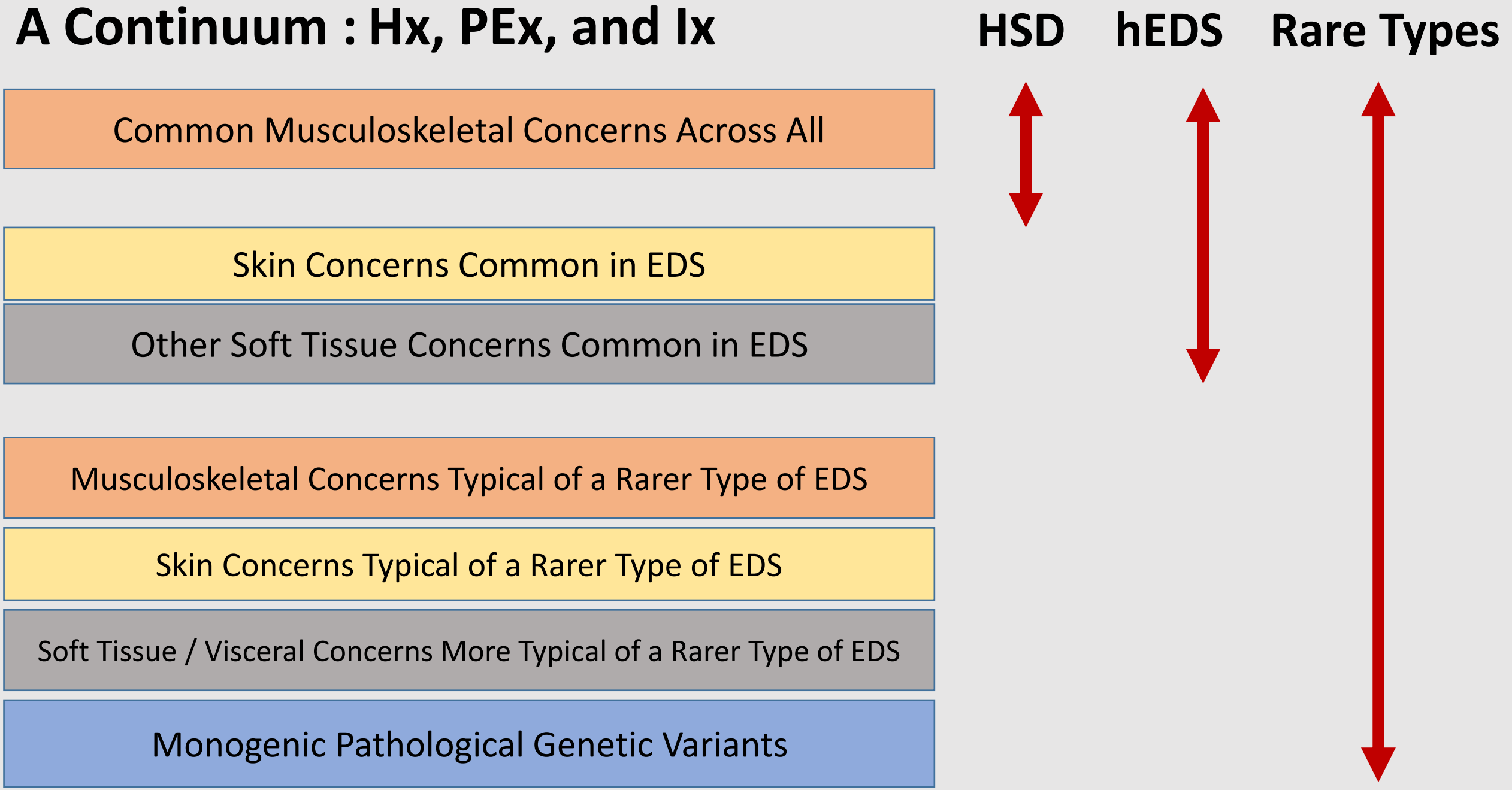
- ☐ Musculoskeletal pain in two or more limbs, recurring daily for at least 3 months
- ☐ Chronic, widespread pain for ≥3 months
- ☐ Recurrent joint dislocations or frank joint instability, in the absence of trauma

**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.

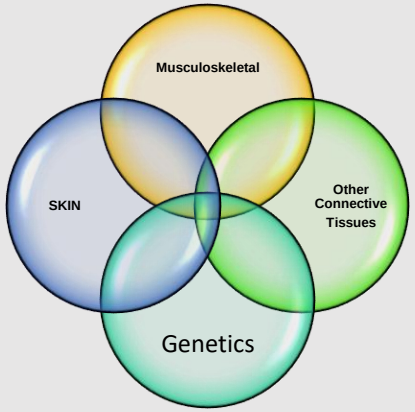
Diagnosis: _____

# A Continuum : Hx, PEx, and Ix



Musculoskeletal

## Findings common to all types of EDS:

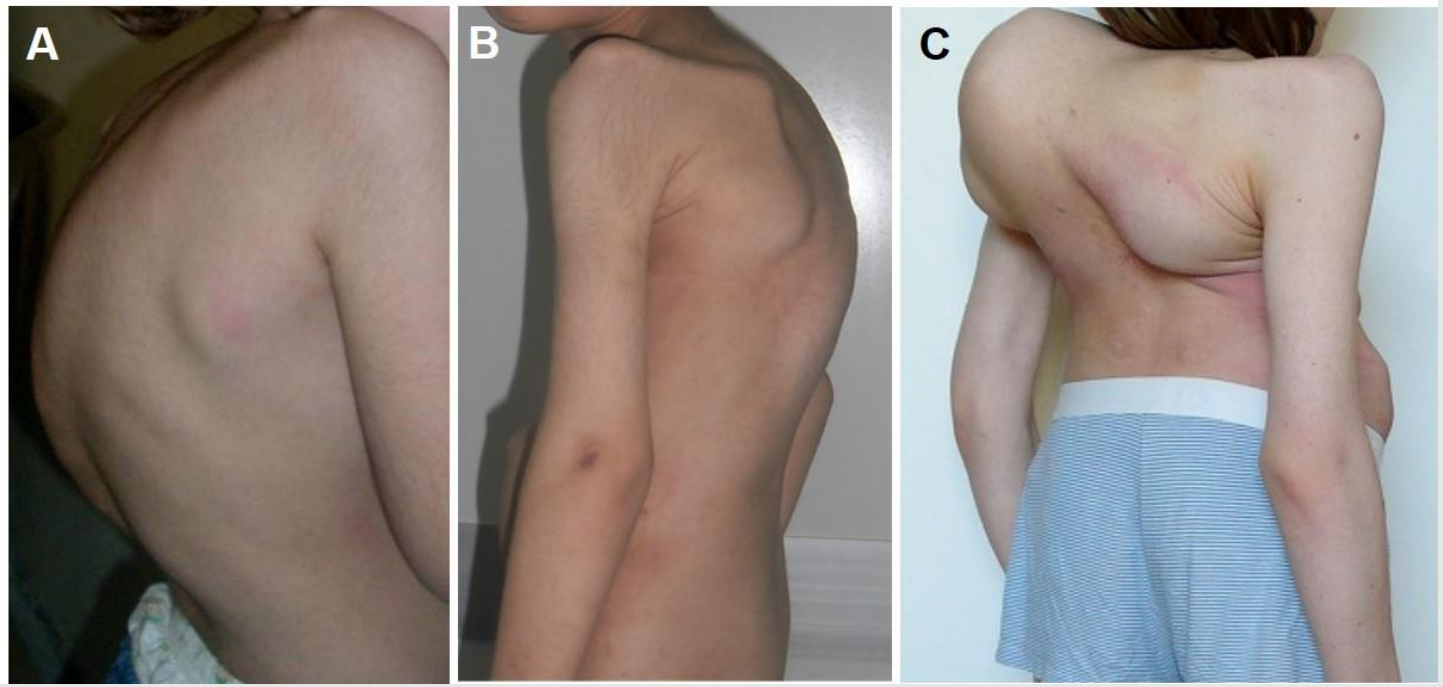


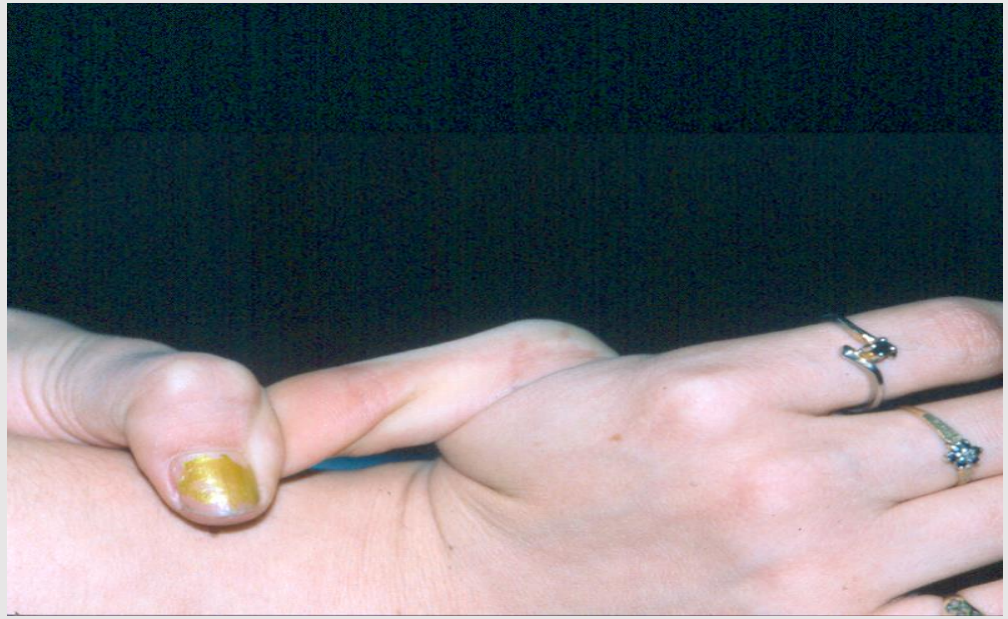

- Generalized Joint Hypermobility
- Joint Instability - Subluxations, Dislocations
- Injury to Ligaments and Tendons, Soft Tissues
- Reduced awareness of position (proprioception)
- Wear on joints – secondary osteoarthritis
- Pain - Joint (arthralgia), Muscle (myalgia), Nerve (neuralgia)

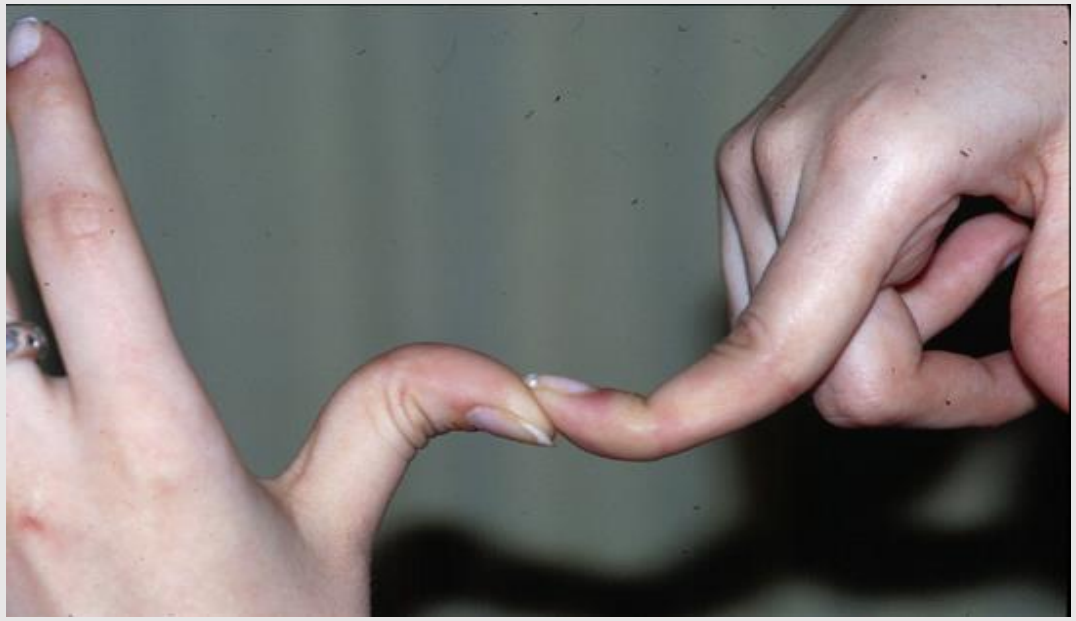
Musculoskeletal

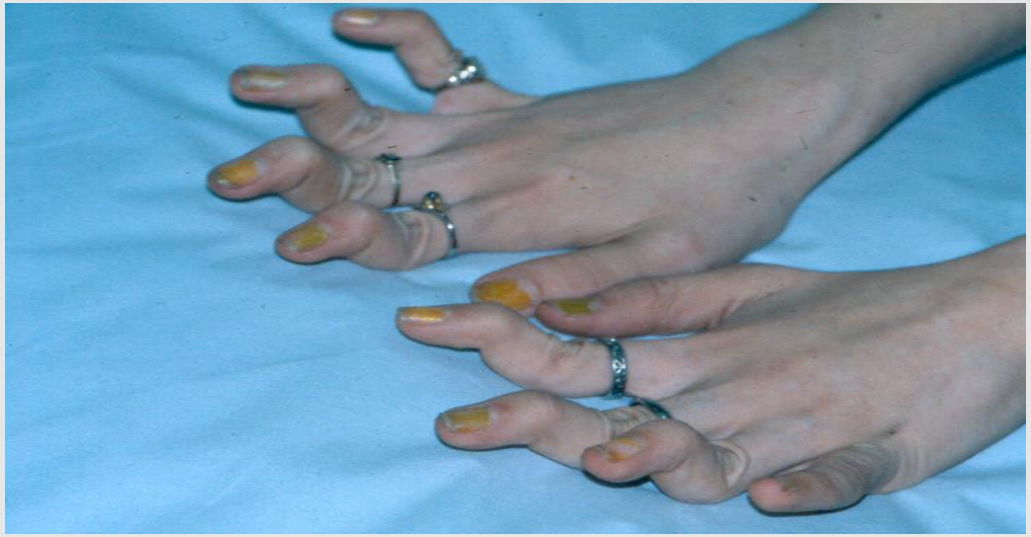
# In rarer types of EDS:

- Severe curvature of the spine – Scoliosis, Kyphosis
- Abnormal joint shape – Dysplasia – e.g., hip
- Dislocations from birth e.g., congenital hip dislocation
- Clubfoot









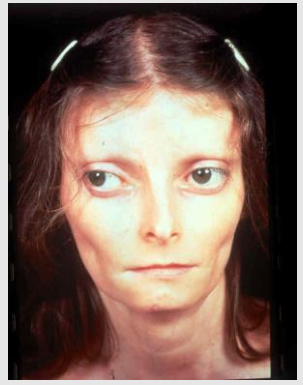
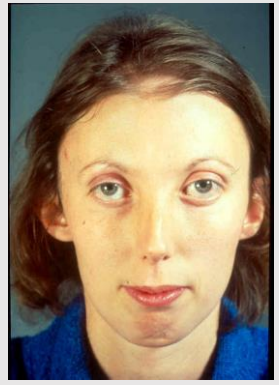
**vEDS, BCS, spEDS, pEDS, mEDS**

**vEDS, clEDS, spEDS, mcEDS**

Musculoskeletal

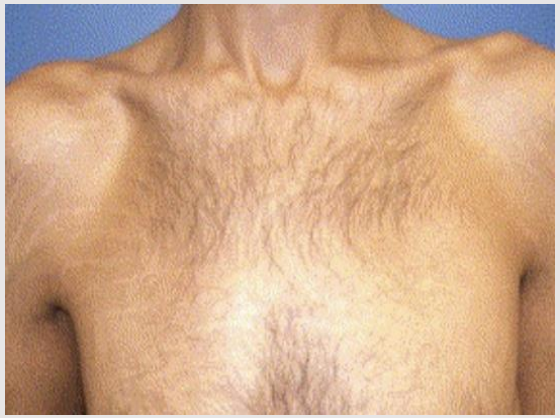
## In rarer types of EDS:

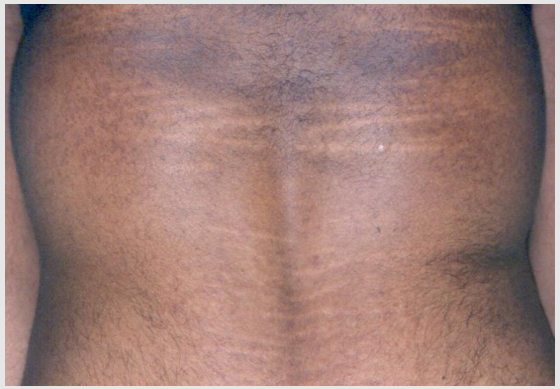
- Changes in skull and facial bone structure, and facial features. e.g. vEDS

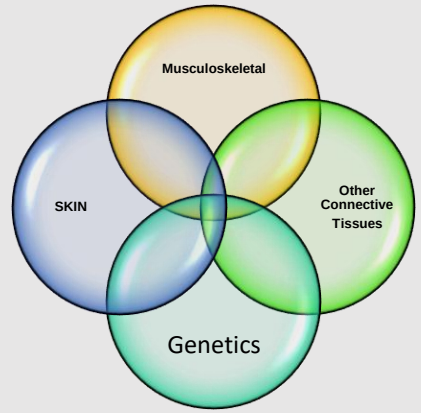

- Short stature
- Low muscle tone from birth – congenital hypotonia
- Tightening of tissues – congenital contractures
- Very low bone density and spontaneous fractures

SKIN



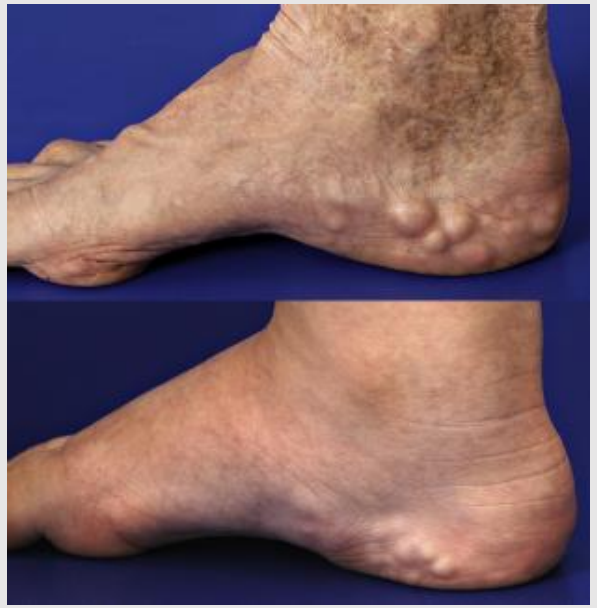


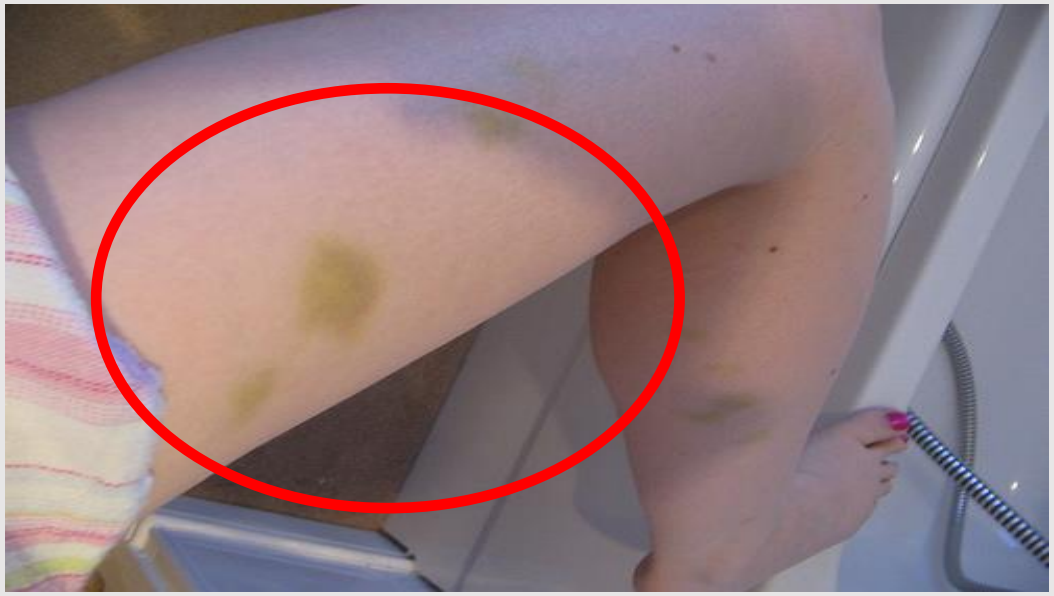
## Findings common to all types of EDS:




- Excessive stretch (elasticity)
- Soft and smooth texture
- Stretch marks from adolescence (excluding causes such as rapid weight gain / loss, steroid treatment)
- Thinned scars – ‘papyraceous’
- Piezogenic papules
- Family history of similar concerns

- Ease of bruising
- Slow wound healing

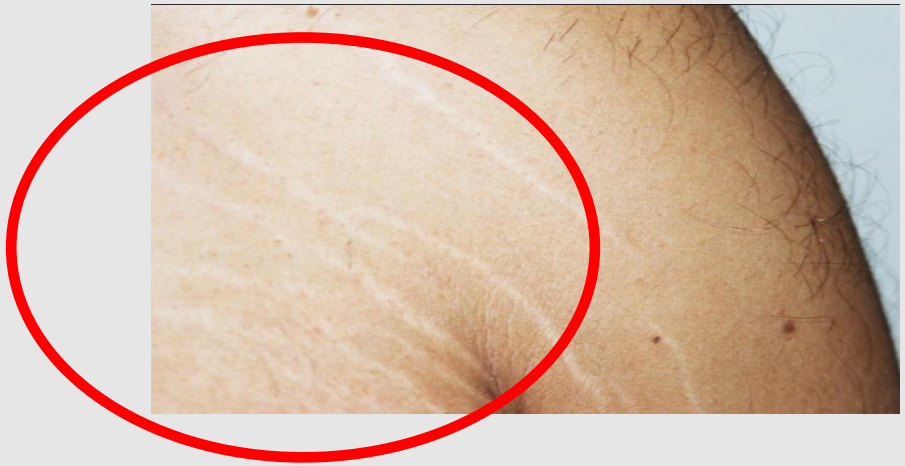


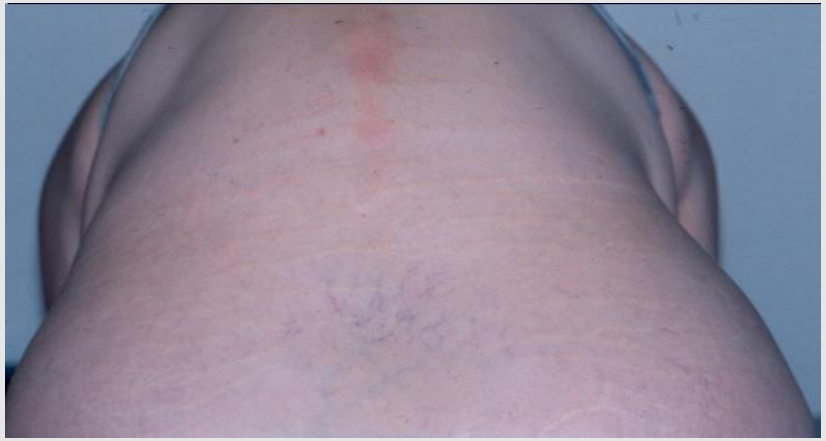


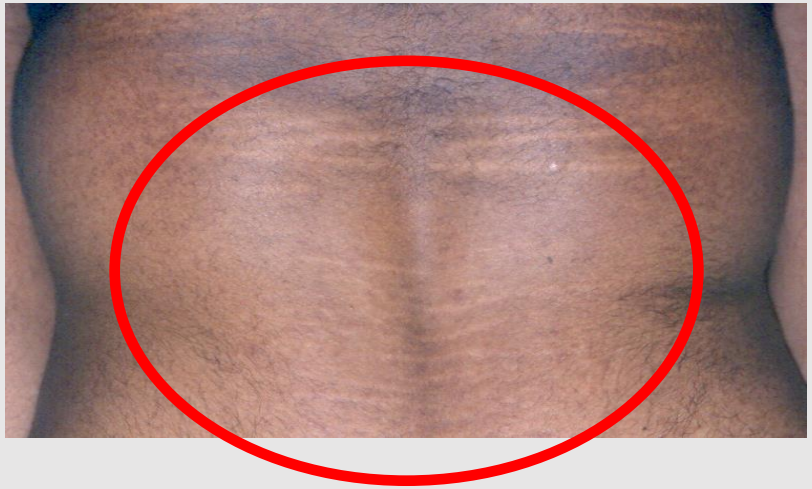
Other Causes of Bruising and Haematomas:

- Steroids
- Cushing's Disease
- Coagulopathy including Platelet dysfunction and deficiencies
- Trauma

# Stretch Marks from Adolescence



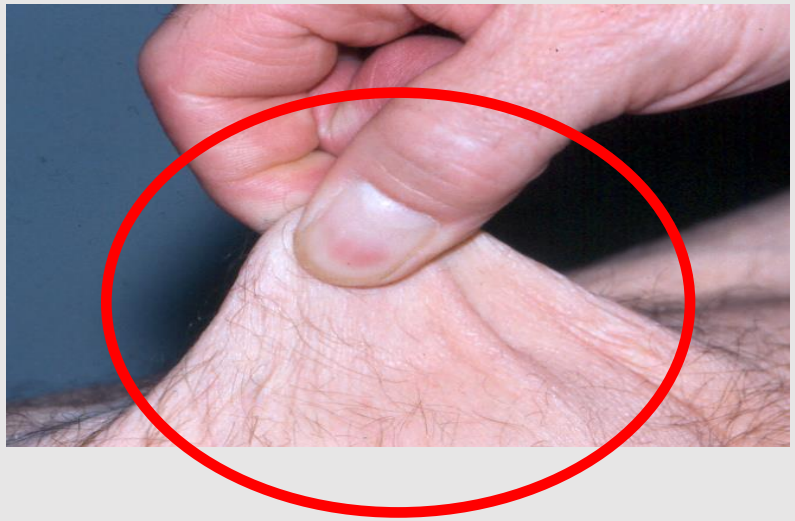


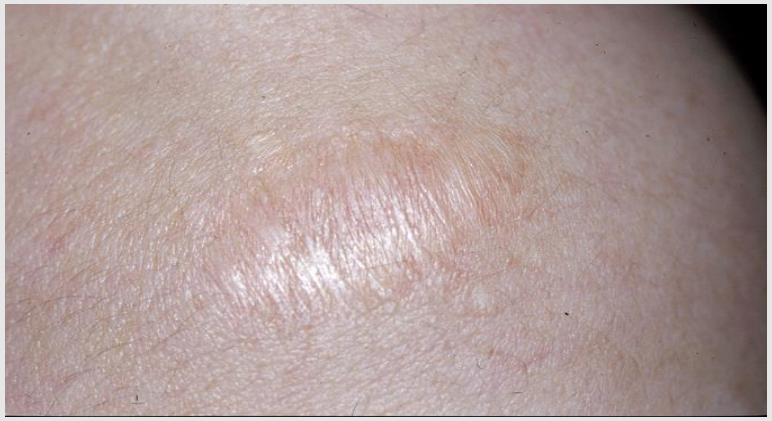


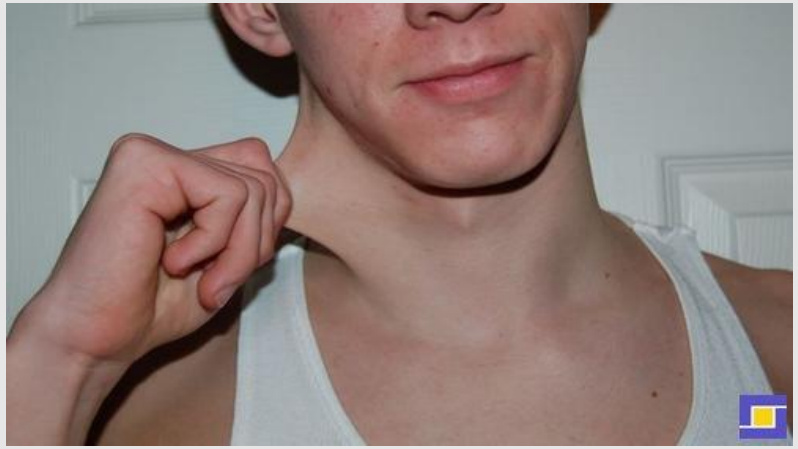
Other Causes:

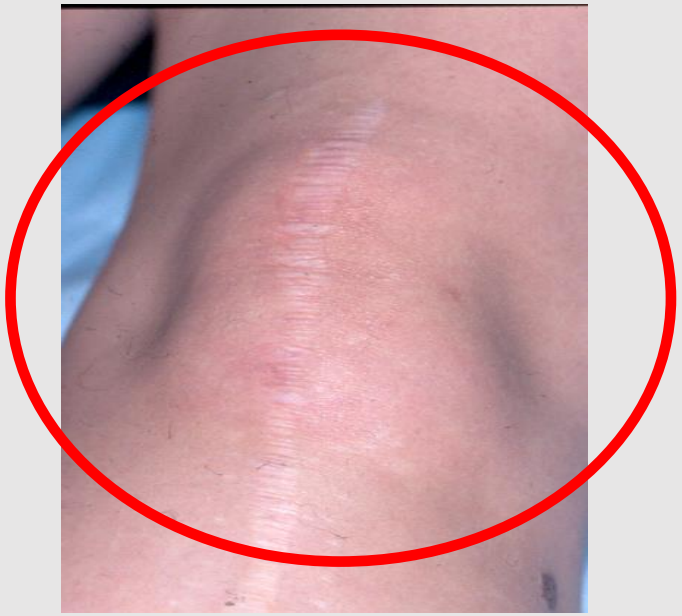
- Obesity
- Pregnancy
- Cushing's Disease
- Steroids
- Skin bleaching

# Excessive skin stretch, papyraceous/atrophic scarring









SKIN

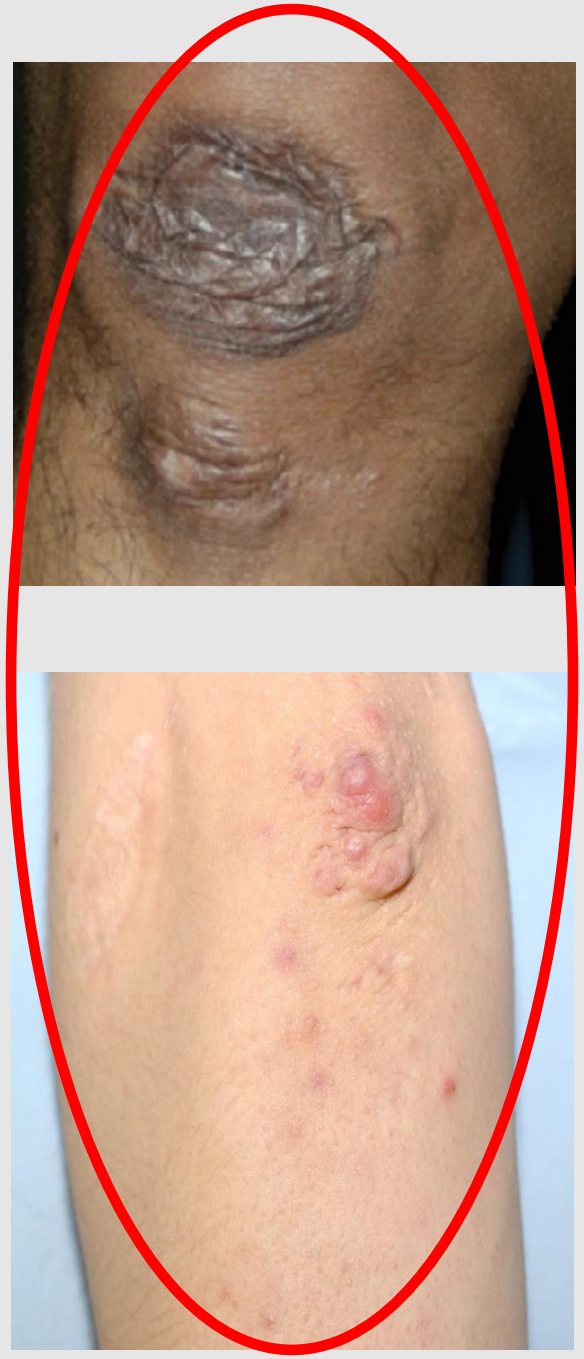
## Seen in the rarer types of EDS

## In cEDS:

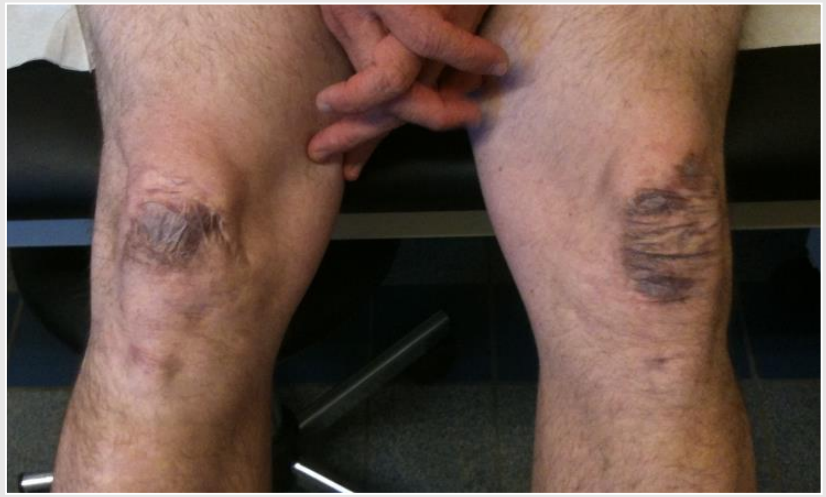
- Very excessive stretch
- Severe haemosiderotic scars
- Molluscoid pseudotumors

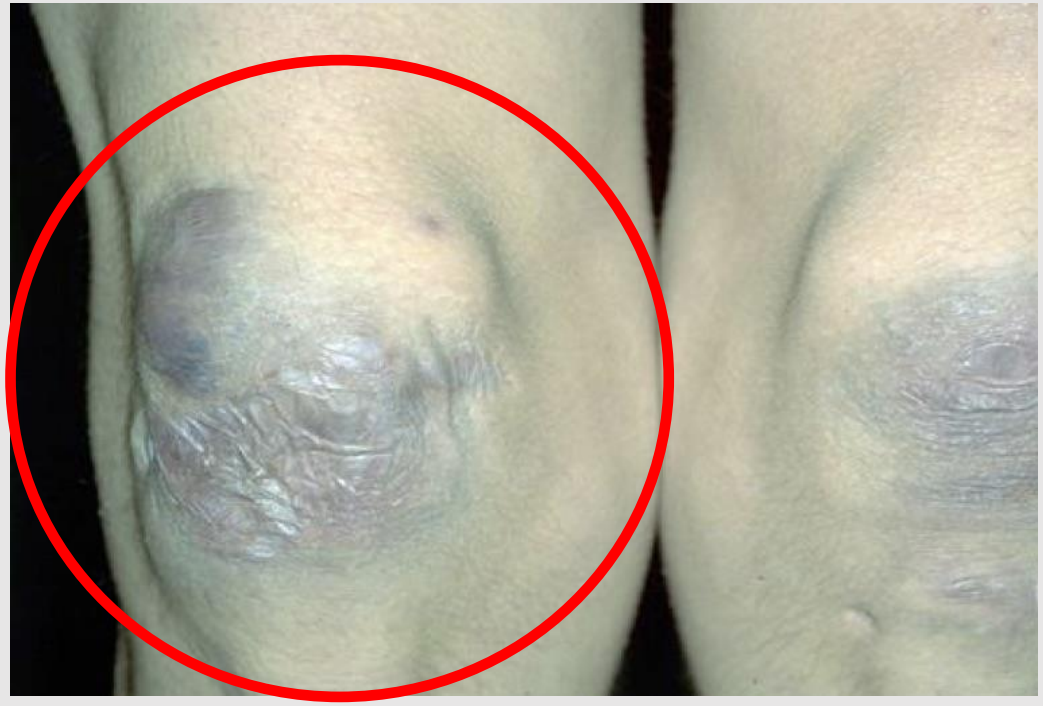
  (spongy nodules – fatty tissue through atrophic scars)
- Subcutaneous spheroids

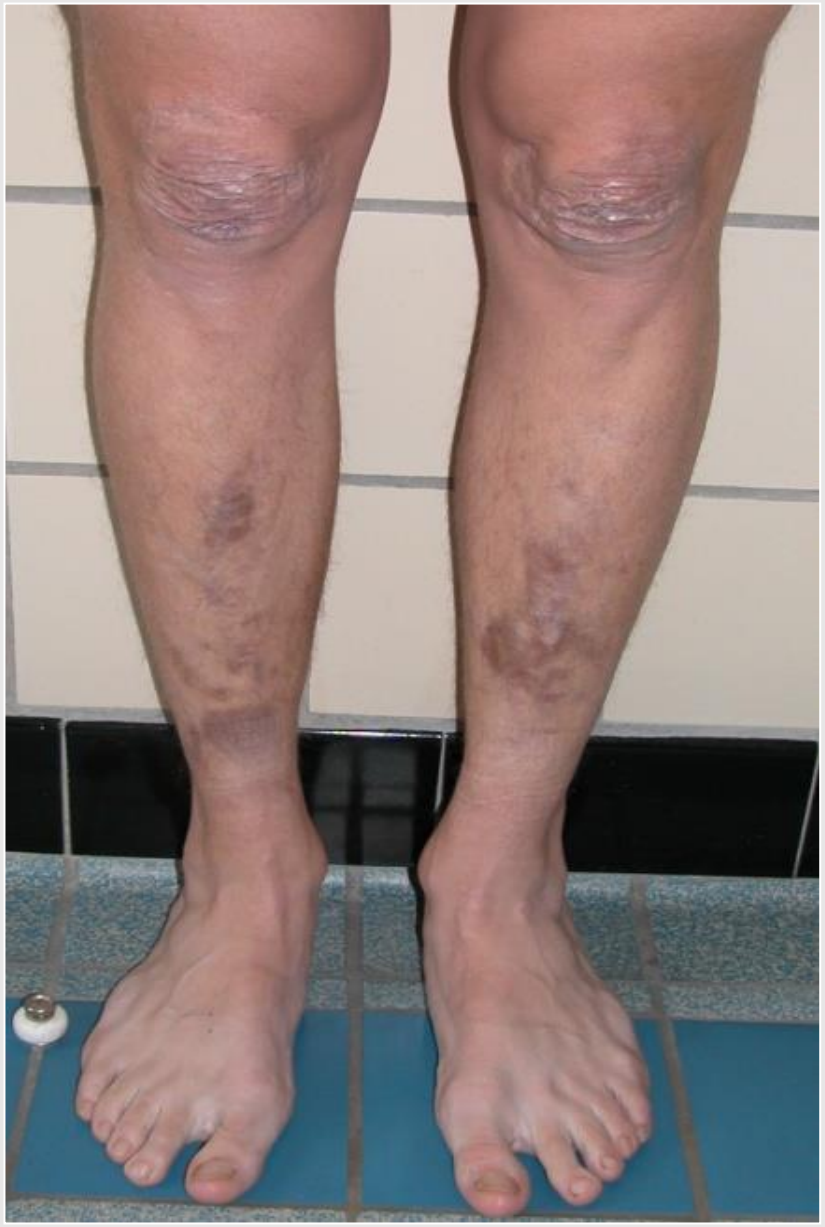
  (small calcified fat lobules (arms and legs)).



# Severe – Atrophic and Haemosiderotic scars



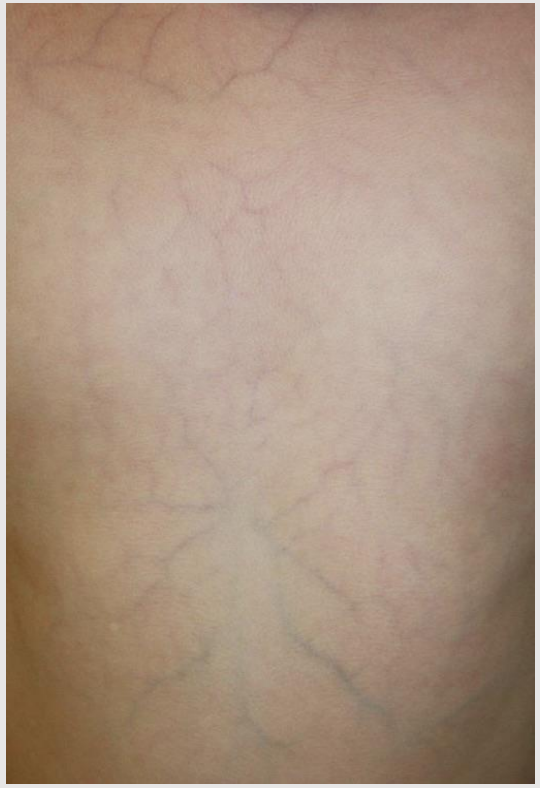


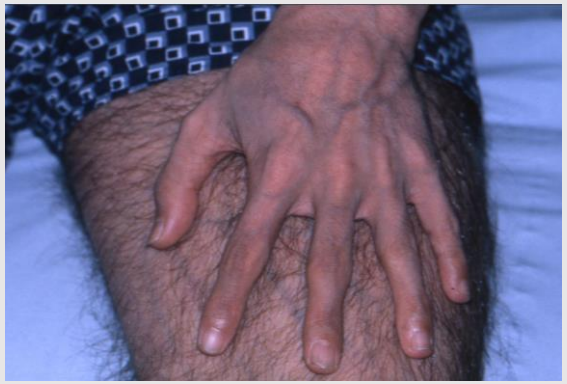


SKIN

## Seen in the rarer types of EDS:

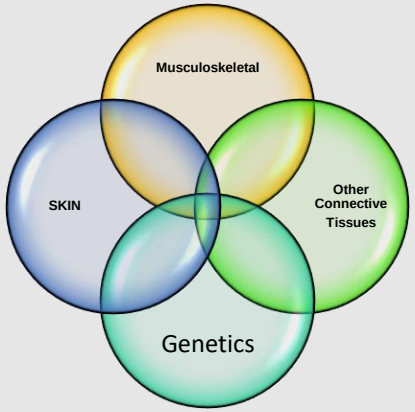
- Severe bruising and haematomas
- Severe varicose veins, typically both legs
- Very thin skin
- Ease of tearing / sloughing skin
- Family history





Other Connective Tissues

**Common - found to varying degrees:**




- **Eyes: short or long-sighted and astigmatism,**
- **Dental crowding / gum disease**
- **Hernias**
- **Gastrointestinal slow transit**
- **Rectal, Bladder, Gynaecological Prolapse**
- **Family History**

Other Connective Tissues

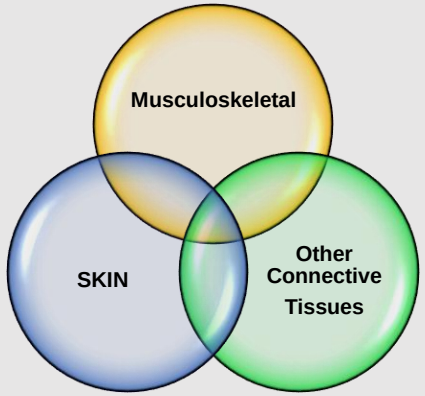
**In some the rarer types of EDS:**

- **Eyes: corneal scarring**
- **Severe gum disease – Peri-odontitis**

**And life-threatening in rarer types of EDS:**

- **Aneurysm, Arterial dissection, Rupture**
- **Bowel and Visceral (organ) Rupture – including uterus in pregnancy**
- **Collapse of lung (pneumothorax)**
- **Aortic Root Dilation - ! Vasculopathies like Marfan Syndrome**
- **Family History**

# Comparing HSD and hEDS




## HSD

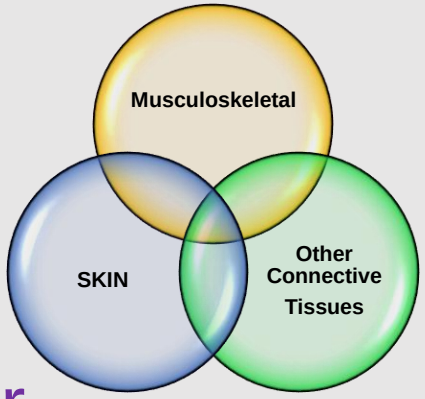
- GJH, LJH, PJH
- JHM – heritable trait
- MSK structural concerns
  - Joint instability
  - Straining / soft tissue injury
- MSK Pain

## hEDS

- GJH
- JHM – heritable trait
- MSK structural concerns
  - Joint instability
  - Straining / soft tissue injury
- MSK Pain

**Both can have related conditions e.g., autonomic, GI etc.**

# Comparing HSD and hEDS

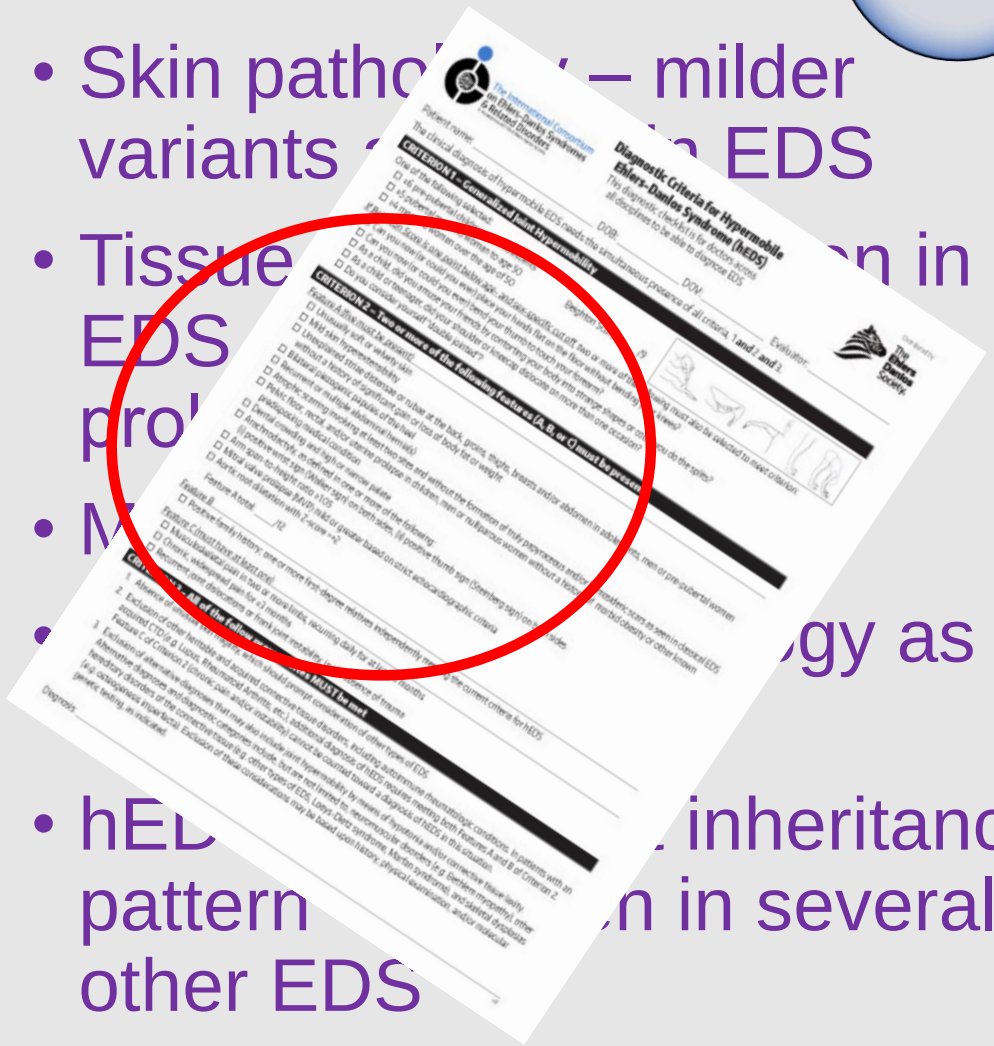



## HSD

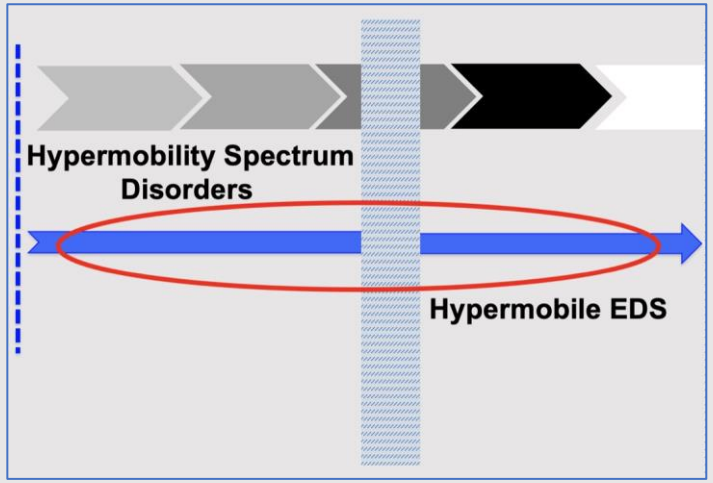
X

## hEDS

- Skin patho – milder variants EDS
- Tissue n in EDS pro
- M
- gy as
- hED inheritance pattern n in several other EDS



# HSD or hEDS?




## HSD

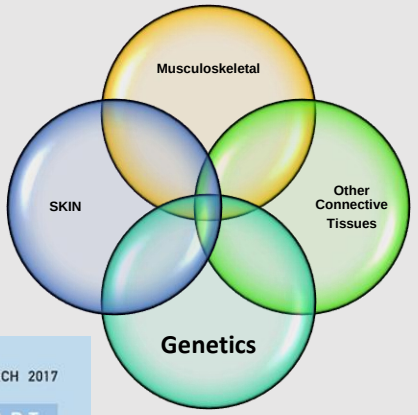
- **GJH**
- **Plus 3 or 4 Criterion 2 signs**
- A few skin signs, and/or a
- Prolapse, and/or
- Marfanoid body shape,

## hEDS

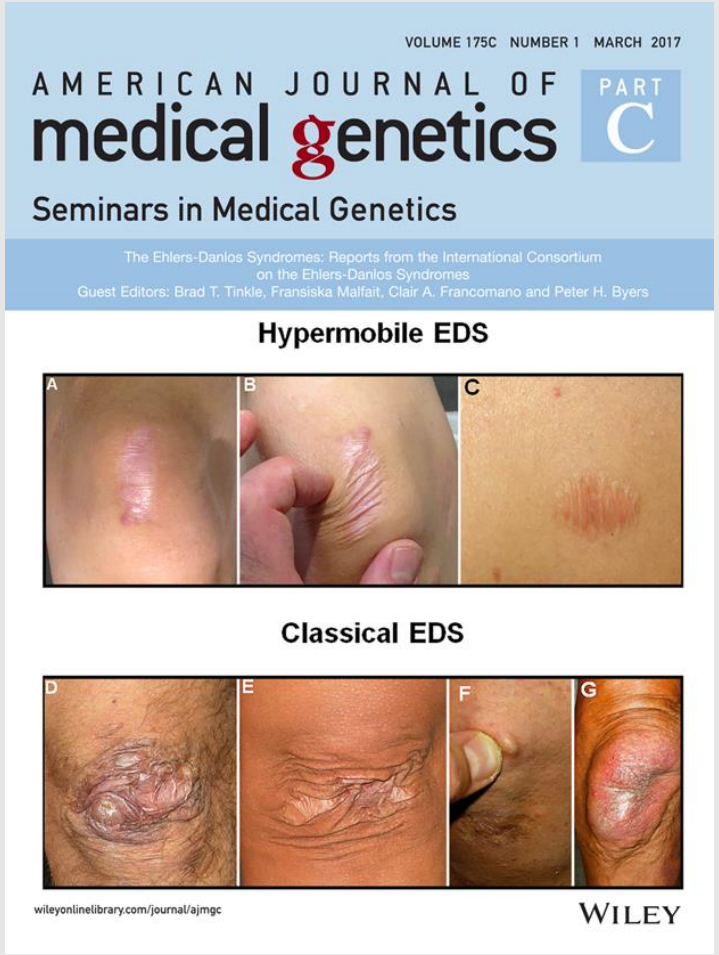
- **GJH**
- Skin pathology – milder variants seen in EDS
- Tissue fragilities seen in EDS – dental, hernia, prolapse…
- Marfanoid body shape
- Cardiac valve pathology

**Treat the person and their problems**

# Genotypes in the 2017 Revised EDS Classification




| | EDS subtype | Inheritance pattern (AD, autosomal dominant; AR, autosomal recessive) | Associated genes |
|---|---|---|---|
| 1 | Classical (cEDS) | AD | *COL5A1, COL5A2* (rarely *COL1A1)* |
| 2 | Classical-like (clEDS) | AR | *TNXB* |
| 3 | Cardiac-valvular (cvEDS) | AR | *COL1A2* |
| 4 | Vascular (vEDS) | AD | *COL3A1* (rarely *COL1A1)* |
| 5 | Hypermobile (hEDS) | AD | Unknown |
| 6 | Arthrochalasia (aEDS) | AD | *COL1A1, COL1A2* |
| 7 | Dermatosparaxis (dEDS) | AR | *ADAMTS2* |
| 8 | Kyphoscoliotic (kEDS) | AR | *PLOD1, FKBP14* |
| 9 | Brittle cornea syndrome (BCS) | AR | *ZNF469, PRDM5* |
| 10 | Spondylodysplastic (spEDS) | AR | *B4GALT7, B3GALT6, SLC39A13* |
| 11 | Musculocontractural (mcEDS) | AR | *CHST14, DSE* |
| 12 | Myopathic (mEDS) | AD/AR | *COL12A1* |
| 13 | Periodontal (pEDS) | AD | *C1R, C1S* |




2018: Variant in *AEBP1* (Blackburn et al, 2018) AND 2020: Variant in COL1A1/A2 (Morlino eta l, 2020)

# Genetic Screening vs Targeted Testing

## Population Prevalence

HSD and EDS –
1 in 500 to 1 in 800

hEDS – 1 in 3200 – 1 in 5000
cEDS – 1 in 20-40000
vEDS – 1 in 1-200000
Others – 1 each in million

## Distribution of Diagnoses

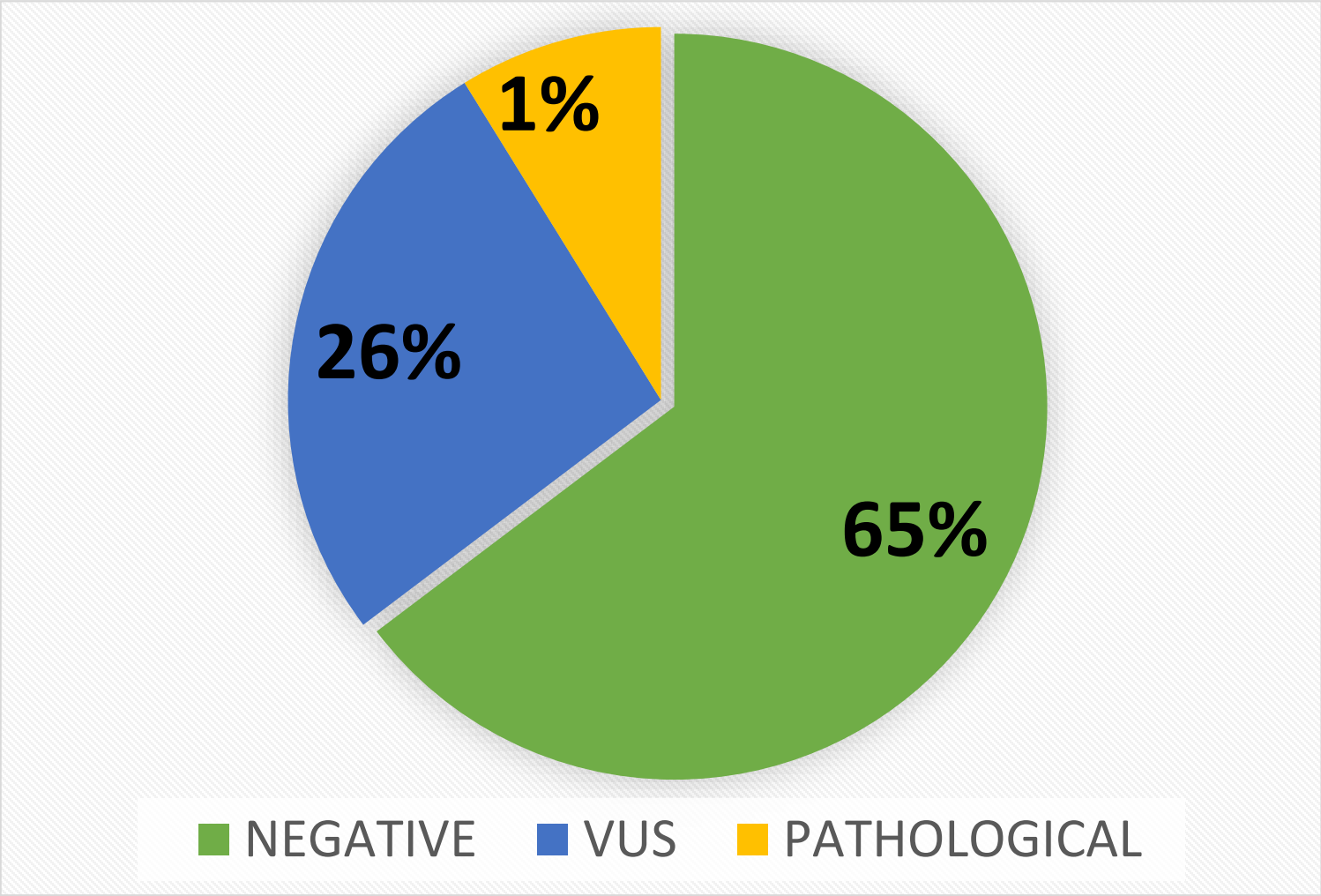
Per Million of the General Population:

2000 with HSD or EDS

382 EDS (20%)

70 Rare type (3-4%)

# My clinic experience of targeted testing



# Ehlers-Danlos Syndromes & Hypermobility Spectrum Disorders

## A Brief Clinical Overview

**Dr. Alan Hakim MB MA FRCP(UK)**

# THANK YOU