Conflict of Interest Disclosures

Welcome to the Central Oregon Medical Society:

"What is Ehlers Danlos Syndrome (EDS) and its Spectrum?"

With Osvaldo Schirripa, MD, MS Central Oregon Clinical Genetics Center

Today's speaker has no relevant financial relationships with ineligible companies to disclose.

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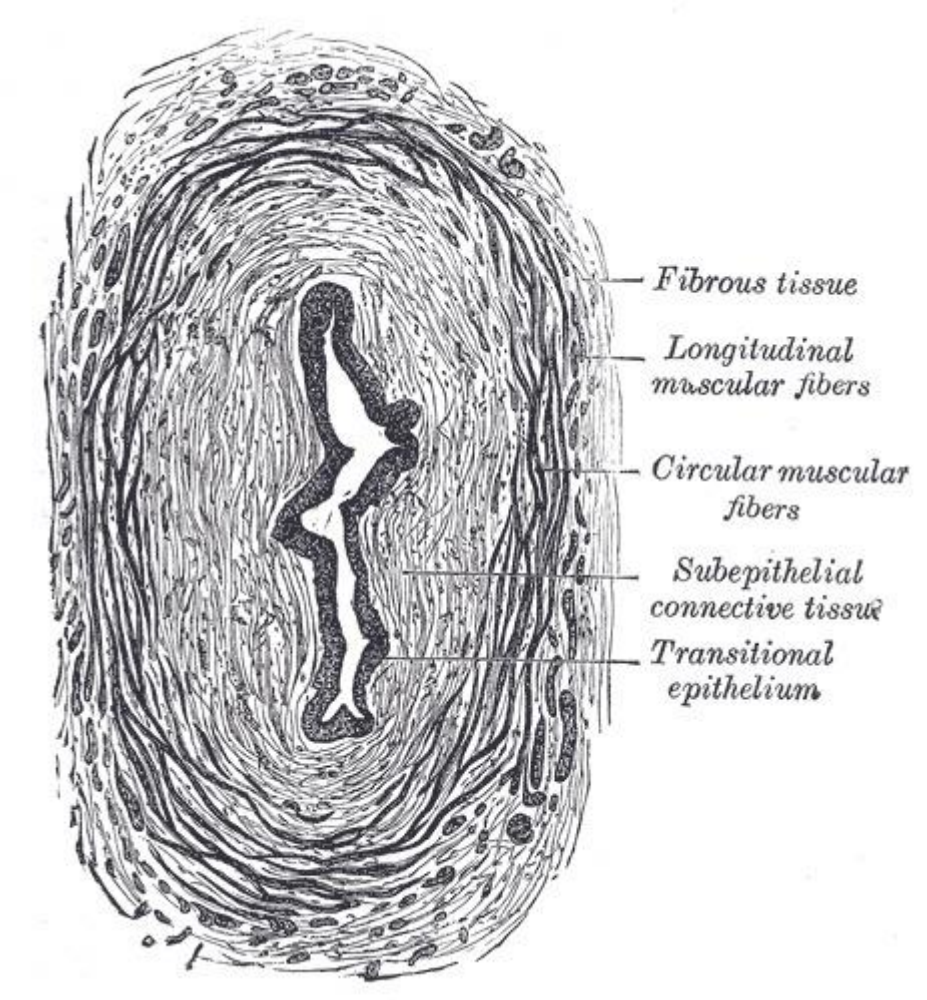
St. Charles

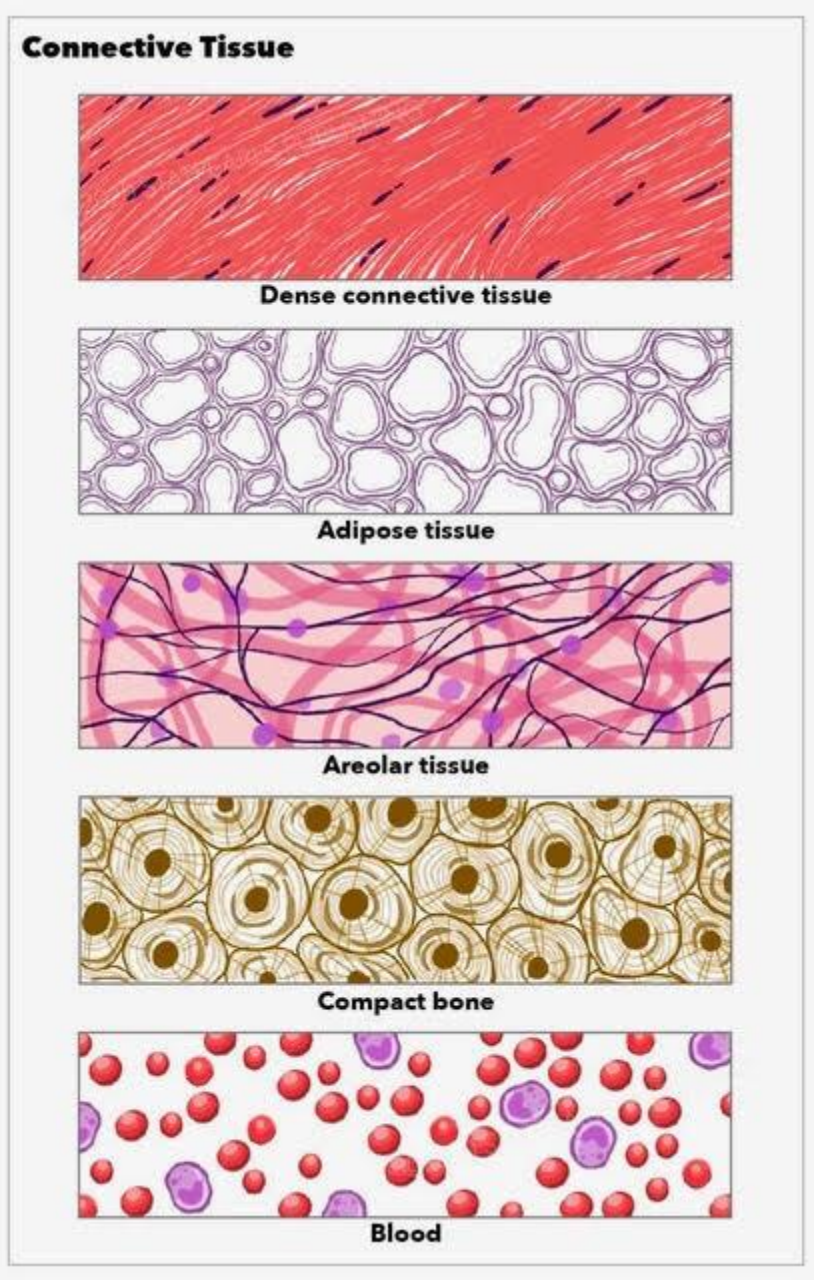
What is Ehlers-Danlos Syndrome (EDS) and It's Spectrum.

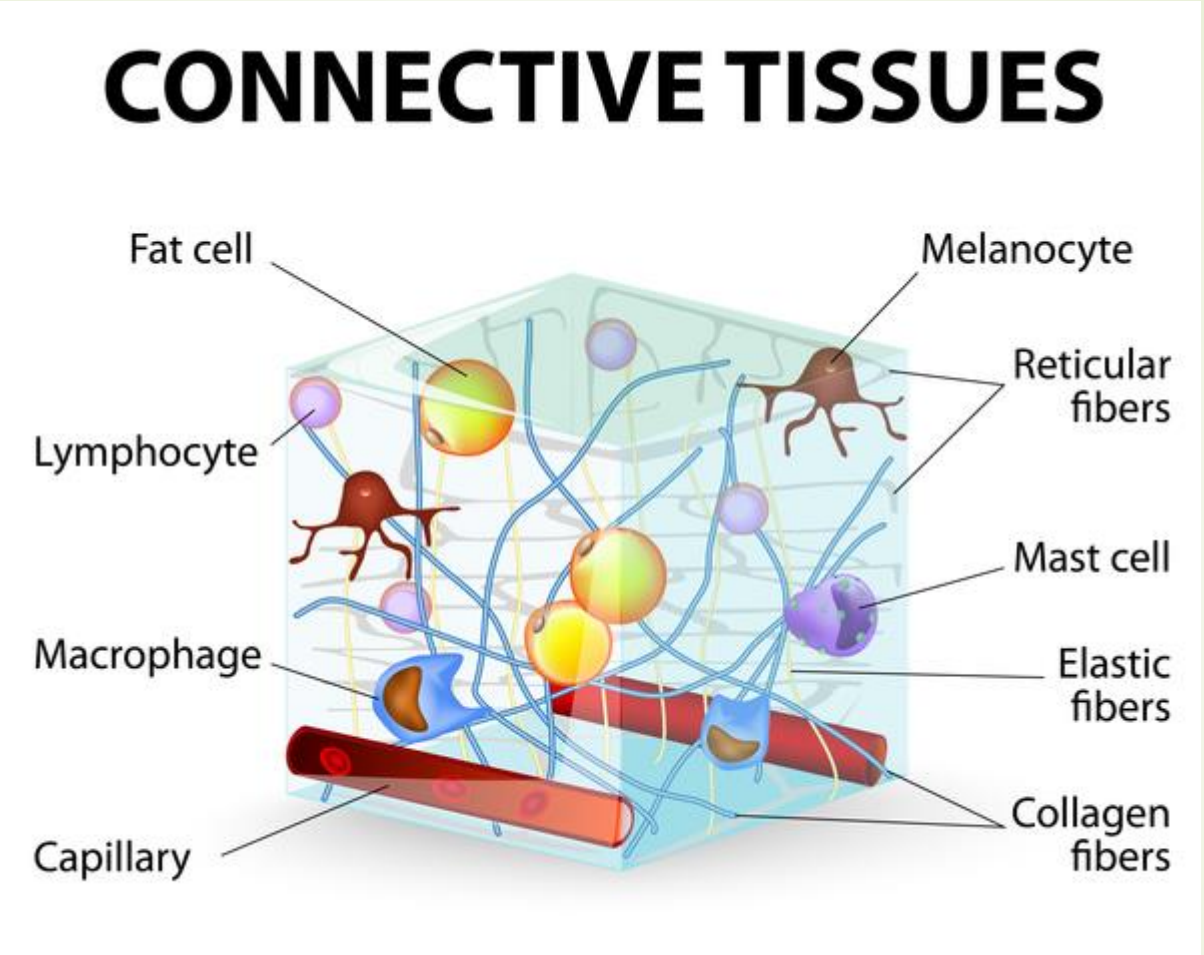
- PubMed Talk presented by Osvaldo Schirripa, MD, MS. Date May 21, 2026
- Central Oregon Clinical Genetics Center
- No Disclosures
- Information presented is publicly available.

What is Ehlers-Danlos Syndrome (EDS) and It's Spectrum.

- Introduction- Review of connective tissue
- History of Ehlers-Danlos Syndrome
- How to identify individuals with Hypermobile Ehlers-Danlos Syndrome
- Connective tissue spectrum:
  - Hypermobile Spectrum Disorder (adult)
  - pGJH/pgHSD
- Q and A
- Information presented is publicly available.

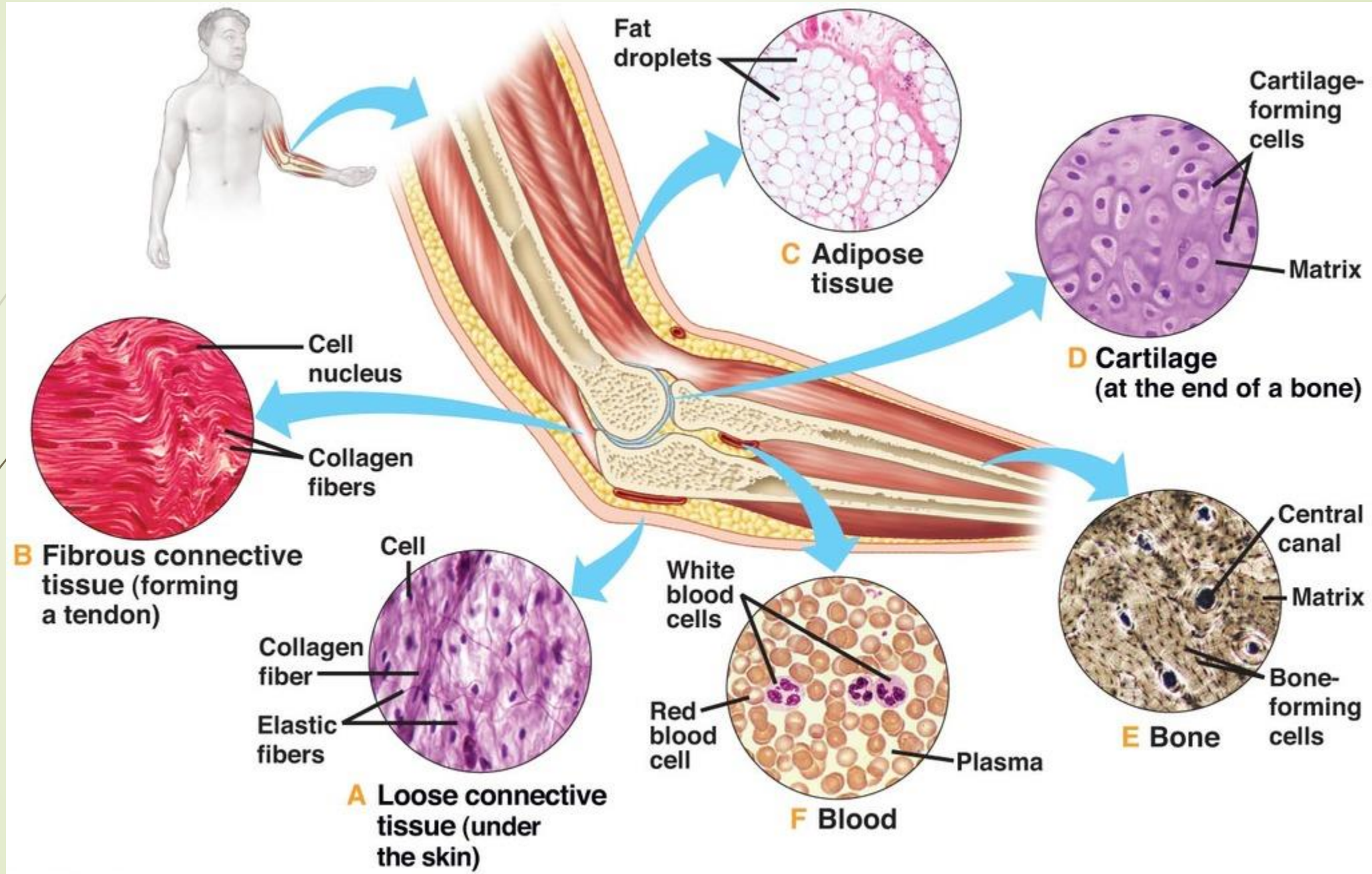

Fibrous tissue
Longitudinal muscular fibers
Circular muscular fibers
Subepithelial connective tissue
Transitional epithelium


Connective Tissue
Dense connective tissue
Adipose tissue
Areolar tissue
Compact bone
Blood



Credit: Designua/Shutterstock.com

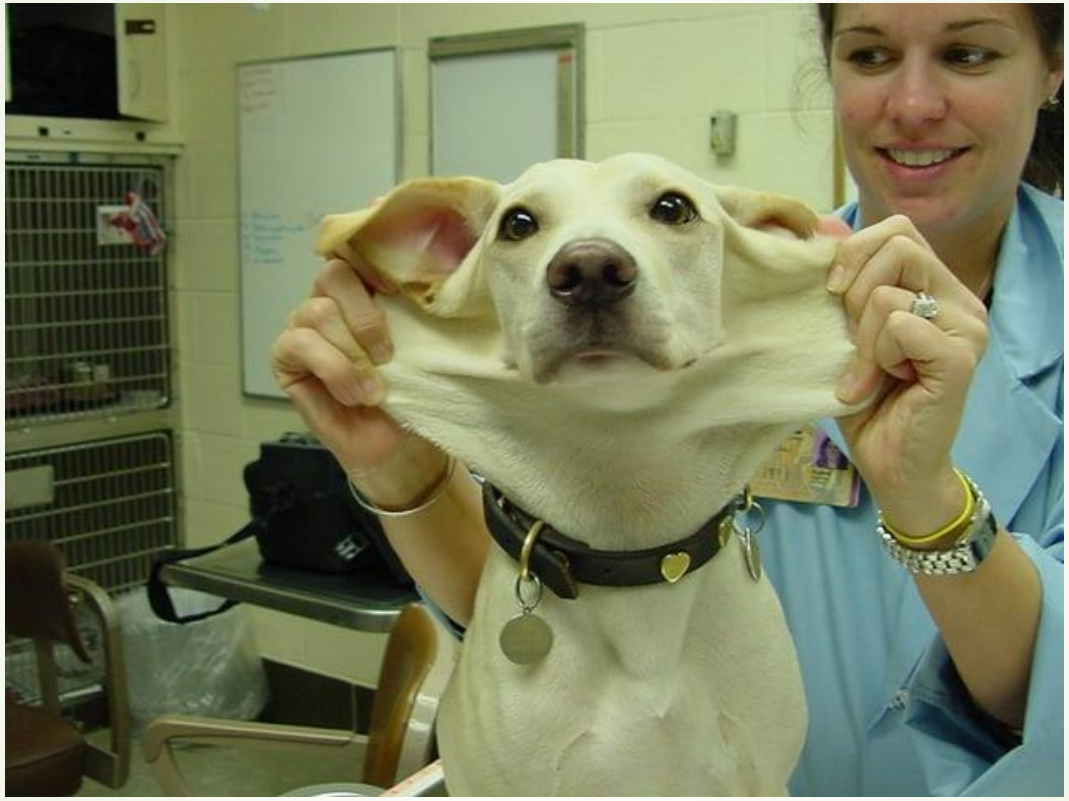
is the tissue that provides structure and strength to the muscles, joints, organs, and skin.



History

- **The Ehlers–Danlos syndromes (EDS) are a heterogeneous group of inherited connective tissue disorders (HCTDs) characterized by:**
  1. **Joint hypermobility,**
  2. **Skin hyper-extensibility**
  3. **Tissue fragility.**
- **The clinical and genetic heterogeneity of this condition has long been recognized**

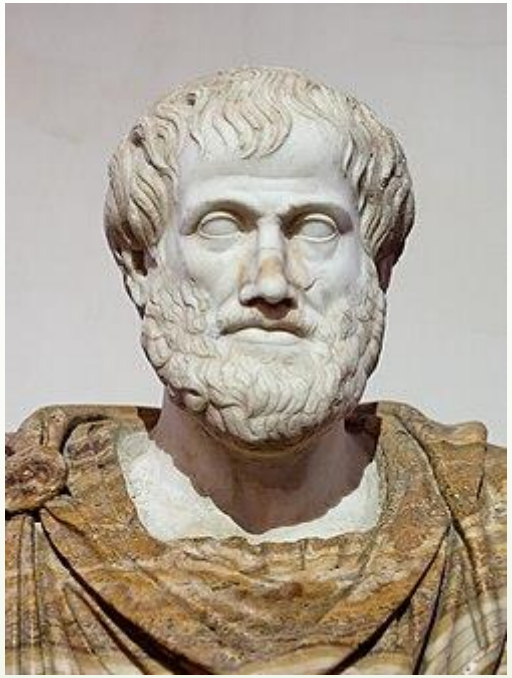
Identifying Individuals with Ehlers-Danlos Syndrome (EDS) and It's Spectrum.



- Over 200 known hereditary connective tissue disorders
- Experimental animals: dogs, mice and zebra fish.

History of EDS

- Ancient Times around **400 BCE**: Hippocrates documented cases of hypermobile joints and stretchy skin. Also, the first to describe bruising and bleeding in these cases.



1800s: Individuals with extreme hypermobility, appeared in circuses as "Human Pretzels"

History of Ehlers Danlos Syndrome

- **1892**: Russian physician (Alexandre Tschernogobow **cher-no-GO-bow**)

published one of the first detailed case studies,

noting abnormal skin and joint laxity.

History of Ehlers Danlos Syndrome

- **1901**: Danish dermatologist Edvard Ehlers described patients with stretchy skin, joint laxity, and easy bruising, recognizing it as a distinct entity.

- **1908**: Henri-Alexandre Danlos emphasized skin extensibility, solidifying the syndrome's recognition, though sometimes confusing it with other conditions.
- **Ehlers-Danlos-Tschernogobow Syndrome**

- **1930s**: Physicians named the disorder, **Ehlers Danlos Syndrome**, while researchers recognized its hereditary nature and different forms.

- **l960s** saw growing recognition of different EDS types, leading to meetings like the 1997 Villefranche-sur-Mer conference, which established six major subtypes.

1998 Am J Med Genetics Apr 28;77(1):31-7. **Ehlers-Danlos syndromes: revised nosology, Villefranche, 1997. Ehlers-Danlos National Foundation (USA) and Ehlers-Danlos Support Group (UK)**

P Beighton 1, A De Paepe, B Steinmann, P Tsipouras, R J Wenstrup

- • **Classical type:** Characterized by soft, velvety, and highly hyperextensible skin alongside widened atrophic scars and generalized joint hypermobility.
- • **Hypermobile type (hEDS):** Focuses on generalized joint hypermobility and joint subluxations/dislocations, along with chronic pain and soft, velvety skin.
- • **Vascular type (vEDS):** The most severe form, marked by thin, translucent skin, severe bruising, and a high risk of arterial, intestinal, or uterine rupture.
- • **Kyphoscoliosis type:** A recessive form involving progressive curvature of the spine, severe generalized joint laxity, and fragile eyes.
- • **Arthrochalasia type:** Distinguished by severe, generalized joint hypermobility with recurrent congenital hip dislocations, and soft, fragile skin.
- • **Dermatosparaxis type:** A rare, severe form known for extreme skin fragility, severe bruising, and sagging skin.

3 Apr 28;77(1):31-7.

History of Ehlers Danlos Syndrome

- **2017** American Journal of Medical Genetics Part C: Seminars in Medical Genetics: Volume 175, Issue 1 March 2017 Pages: i, 1-245

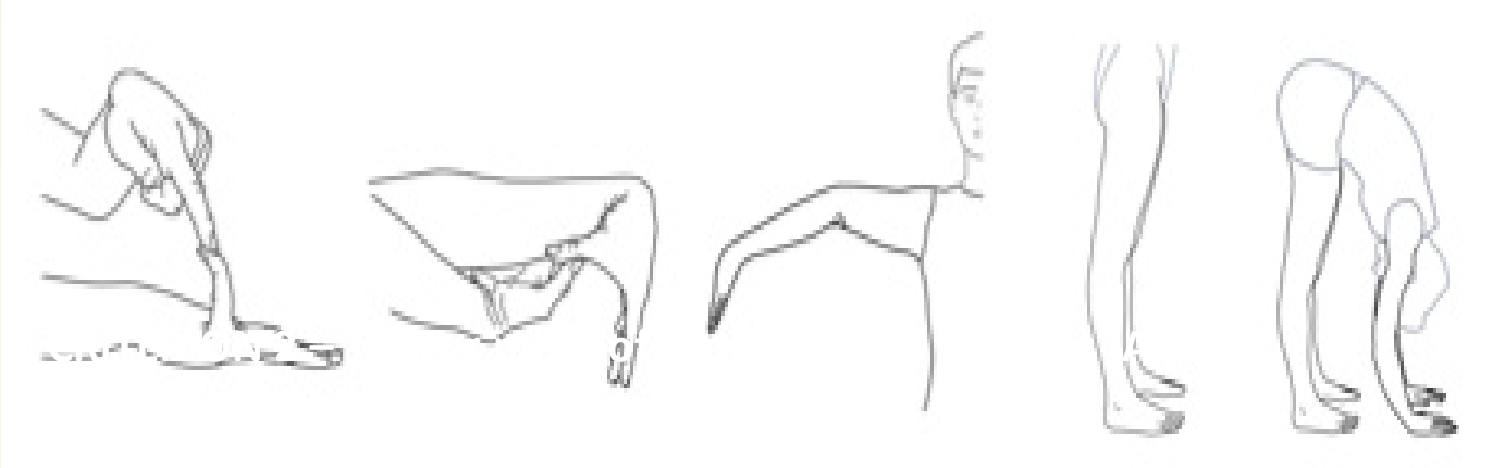
  Classification: An international consortium created the classification, defining 13 types of EDS and included in this classification were six types of hypermobile spectrum disorders.

  Special Issue:The Ehlers-Danlos Syndromes: Reports from the International Consortium on the Ehlers-Danlos Syndromes

- **2023**: For pediatrics individuals, ages 18 years and younger, the international EDS society added 8 types of hypermobility spectrum disorders.
- https://www.ehlers-danlos.com/what-is-eds/

The diagnosis of adult hypermobile EDS has to meet the presence of three criteria.

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

Goniometer

CRITERION 2 – Two or more of the following features (A, B, or C) must be present

Feature A (five of 12 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

VOLUME 175C NUMBER 1 MARCH 2017

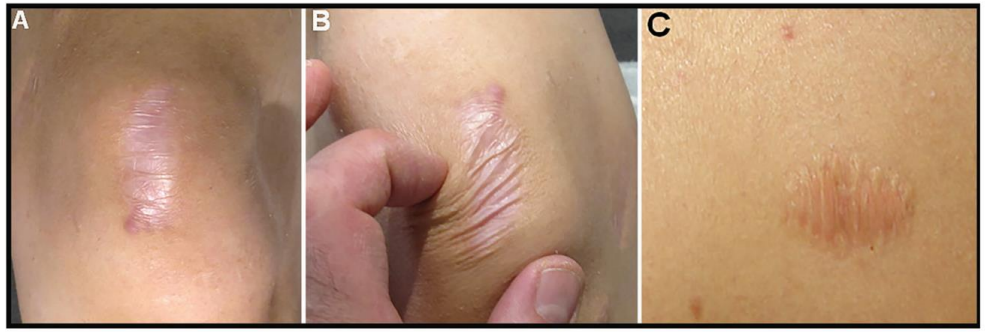
AMERICAN JOURNAL OF medical genetics PART C

Seminars in Medical Genetics

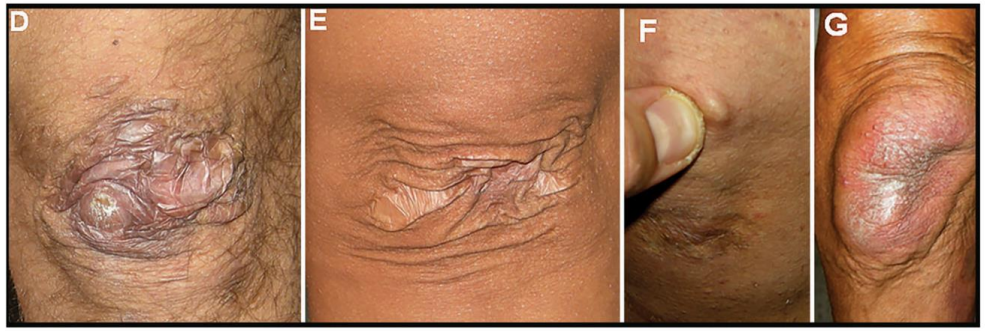
The Ehlers-Danlos Syndromes: Reports from the International Consortium on the Ehlers-Danlos Syndromes

Guest Editors: Brad T. Tinkle, Fransiska Malfait, Clair A. Francomano and Peter H. Byers

Hypermobile EDS



Classical EDS



wileyonlinelibrary.com/journal/ajmgc

WILEY

CRITERION 2
Feature A continue

- 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

CRITERION 2
Continue

- **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 must be meet.

- 1. Absence of unusual skin fragility, 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. In 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.

Additional questions to include: 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"?

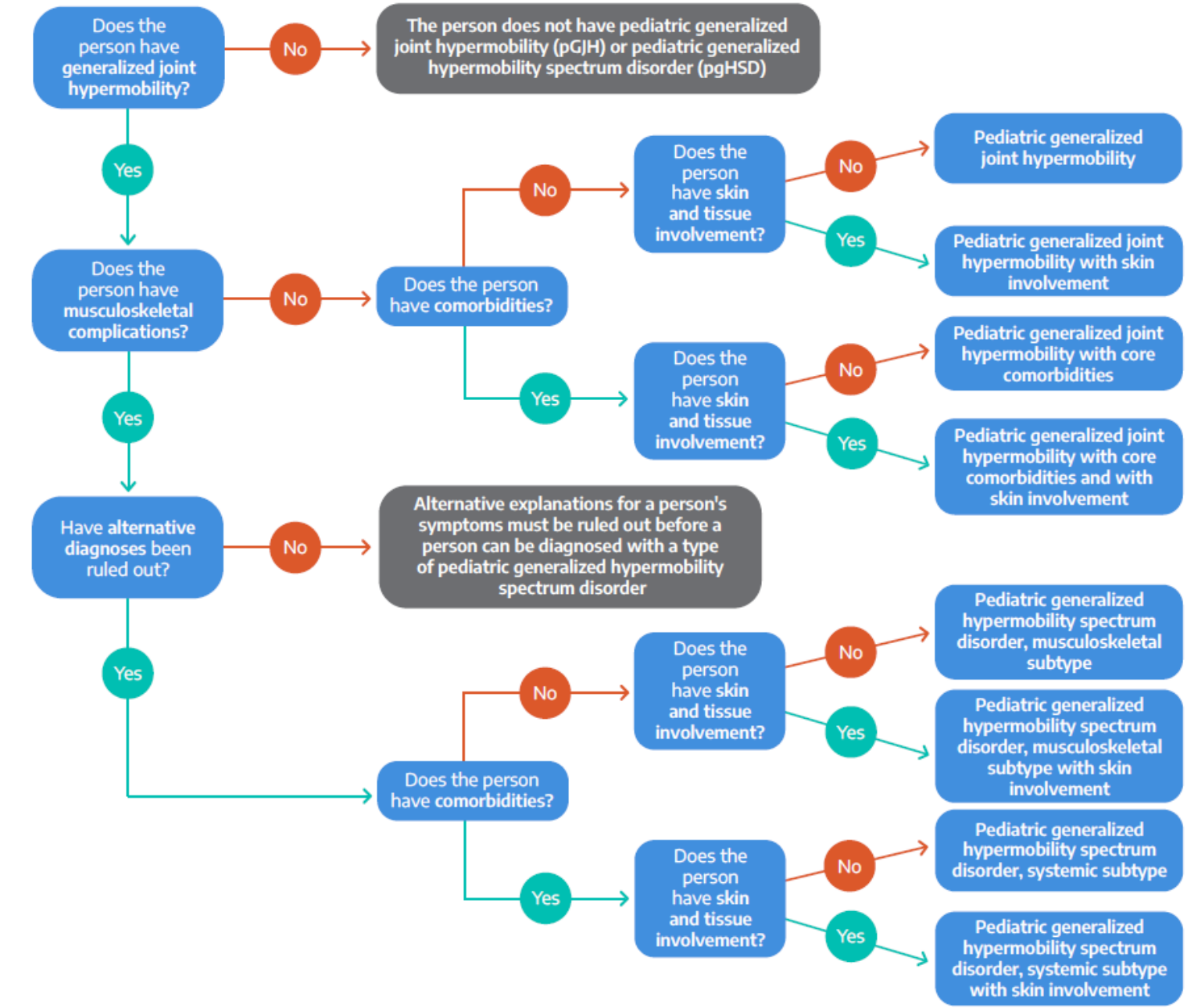
Name of EDS Subtype	IP*	Genetic Basis	Protein involved
Classical EDS (cEDS)	AD	Major: *COL5A1, COL5A2*	Type V collagen
		Rare: *COL1A1* c.934C>T, p.(Arg312Cys)	Type I collagen
Classical-like EDS (clEDS)	AR	*TNXB*	Tenascin XB
Cardiac-valvular EDS (cvEDS)	AR	*COL1A2* (biallelic mutations that lead to *COL1A2* NMD and absence of pro α2(I) collagen chains)	Type I collagen
Vascular EDS (vEDS)	AD	Major: *COL3A1*	Type III collagen
		Rare: *COL1A1* c.934C>T, p.(Arg312Cys) c.1720C>T, p.(Arg574Cys) c.3227C>T, p.(Arg1093Cys)	Type I collagen
Hypermobile EDS (hEDS)	AD	Unknown	Unknown
Arthrochalasia EDS (aEDS)	AD	*COL1A1, COL1A2*	Type I collagen
Dermatosparaxis EDS (dEDS)	AR	*ADAMTS2*	ADAMTS-2
Kyphoscoliotic EDS (kEDS)	AR	*PLOD1*	LH1
		FKBP14	FKBP22
Brittle cornea syndrome (BCS)	AR	*ZNF469*	ZNF469
		PRDM5	PRDM5
Spondylodysplastic EDS (spEDS)	AR	*B4GALT7*	β4GalT7
		B3GALT6	β3GalT6
		SLC39A13	ZIP13
Musculocontractural EDS (mcEDS)	AR	*CHST14*	D4ST1
		DSE	DSE
Myopathic EDS (mEDS)	AD or AR	*COL12A1*	Type XII collagen
Periodontal EDS (pEDS)	AD	*C1R*	C1r

The Spectrum of Joint Hypermobility

Type	*Beighton score*	*Musculoskeletal involvement**	*Notes*
Asymptomatic generalized JH	Positive	Absent	
Asymptomatic peripheral JH	Usually negative	Absent	JH typically limited to hands and/or feet
Asymptomatic localized JH	Negative	Absent	JH limited to single joints or body parts
Generalized-HSD	Positive	Present	
Peripheral-HSD	Usually negative	Present	JH typically limited to hands and/or feet
Localized-HSD	Negative	Present	JH limited to single joints or body parts
Historical-HSD	Negative	Present	Historical presence of JH
hEDS	Positive	Possible	

Musculoskeletal involvement includes trauma (micro- and macrotrauma), chronic pain, disturbed proprioception, and other traits (flat feet, misaligned bones in the elbow and big toe, mild-to-moderate scoliosis, kyphosis (outward curvature) of the upper spine, lordosis (inward curvature) of the lower spine.

PEDIATRIC DIAGNOSTIC FLOWCHART



Basics of Diagnosis for pgHSD/HSD/EDS Spectrum

- Diagnosing Pediatric Generalized Joint Hypermobility/ Pediatric Generalized Hypermobile Spectrum Disorder
- infants and toddlers up to age 5 years have insufficient bony maturity for clinically meaningful assessment.
- Biological maturity is defined as skeletal maturity with growth velocity less than 1 cm/year using 2 measures at least 3 months apart, or a mature bone age x-ray.
- Adolescents who reach biological maturity before 18 years old, and young adults aged 18 years and over should be reassessed against the current 2017 criteria.

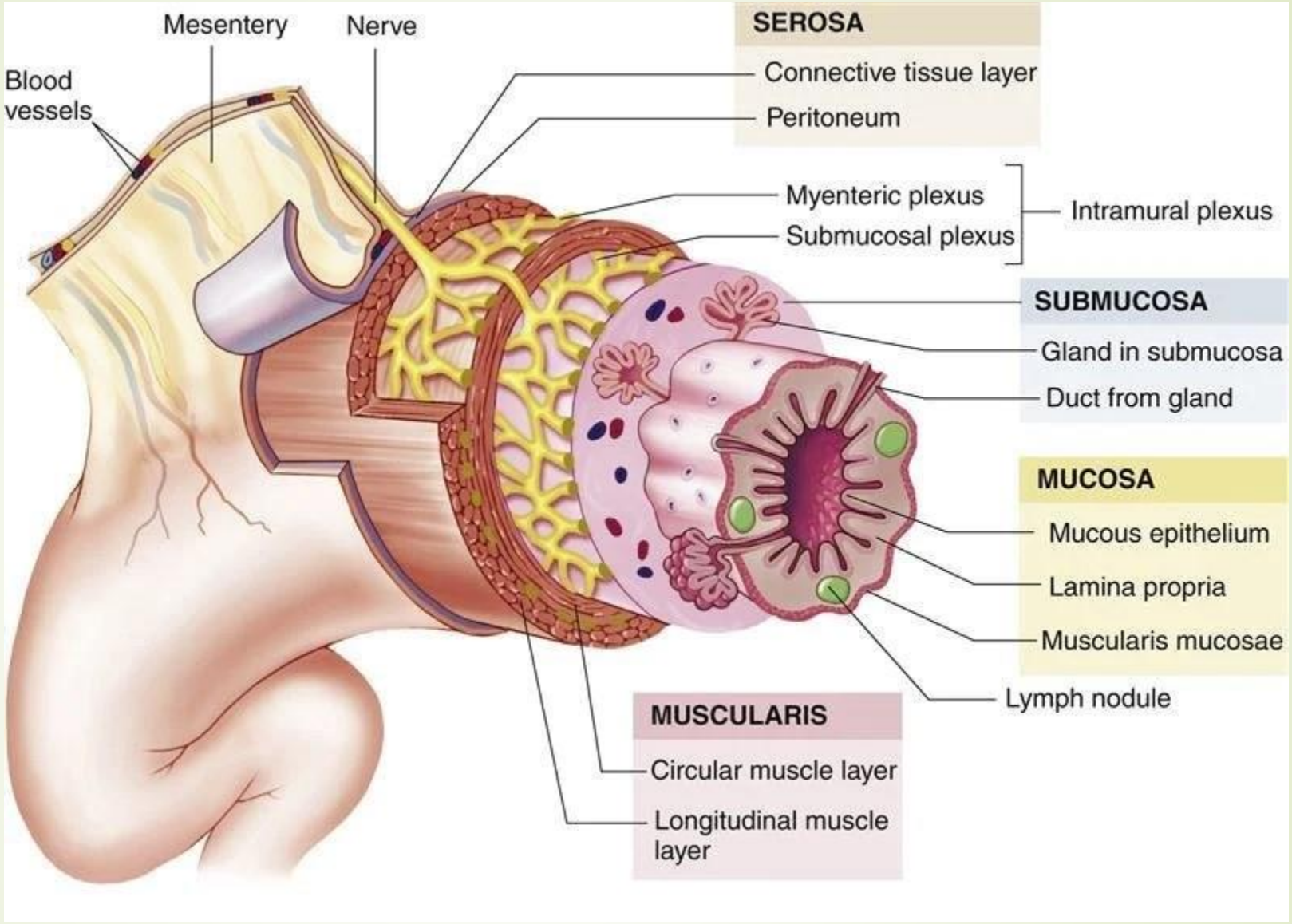
Questions

- **When to refer?**
  - **Very important**: Neurodivergence and LGBTQIA+
  - In individuals with failure to thrive as child with digestive issues:
    - Adverse food reactions, neonatal onset, active.
    - Food protein-induced enterocolitis syndrome
    - Gastrointestinal food allergy, toddler onset, active.
    - Avoidant/Restrictive Food Intake disorder ARFIDI
    - Enteroception is integrated in sensory, emotional, cognitive, and motivational representations.
  - When to refer: eg. Need to differentiate pre-diabetic from non-diabetic hypoglycemia.
  - Alice in Wonderland syndrome (AIWS) is a neurological disorder that distorts perception of size, shape, time, and other senses

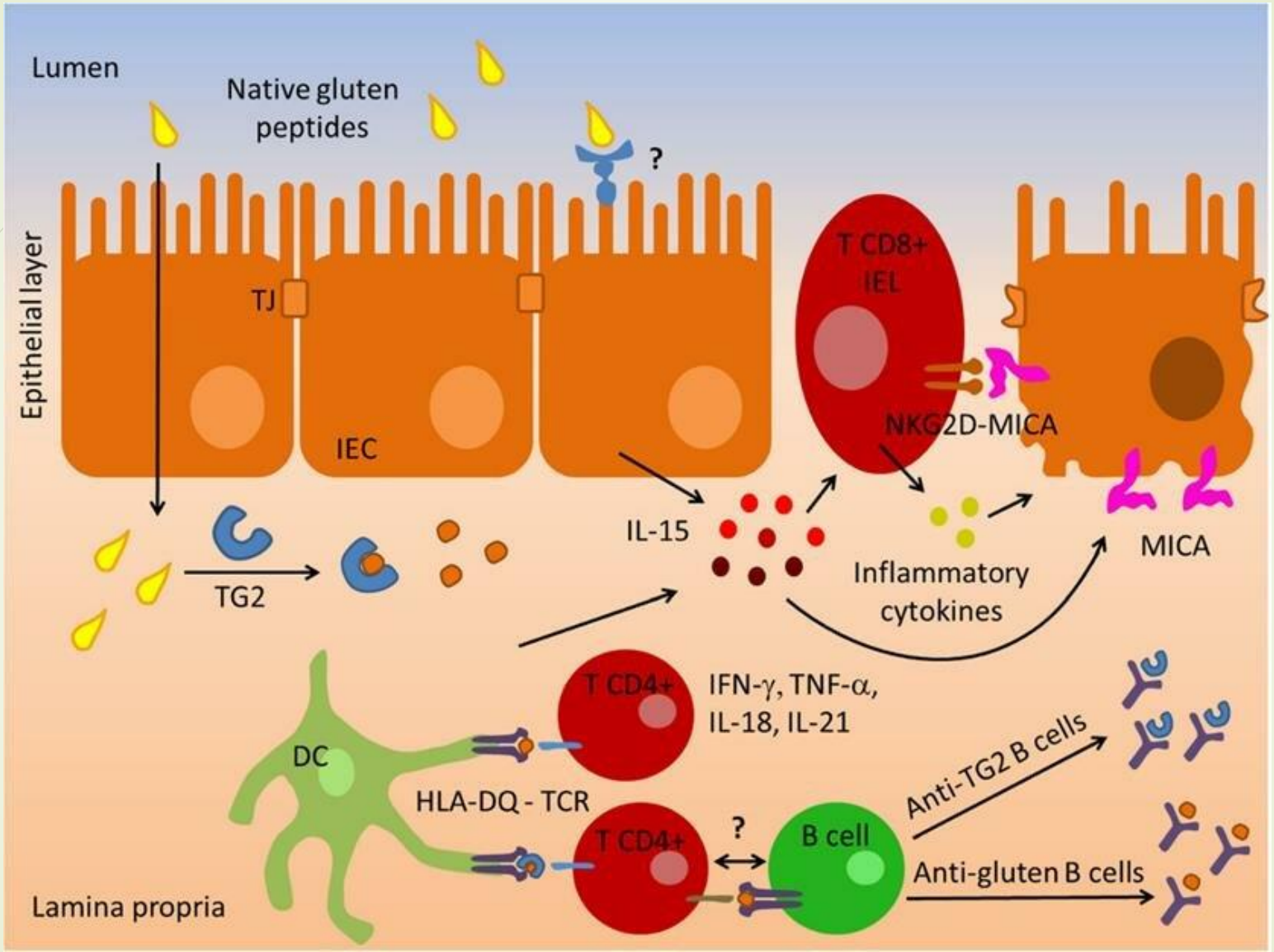
    verses Hallucinogen Persisting Perception Disorder
- **Misdiagnosis is not uncommon.**

Questions?

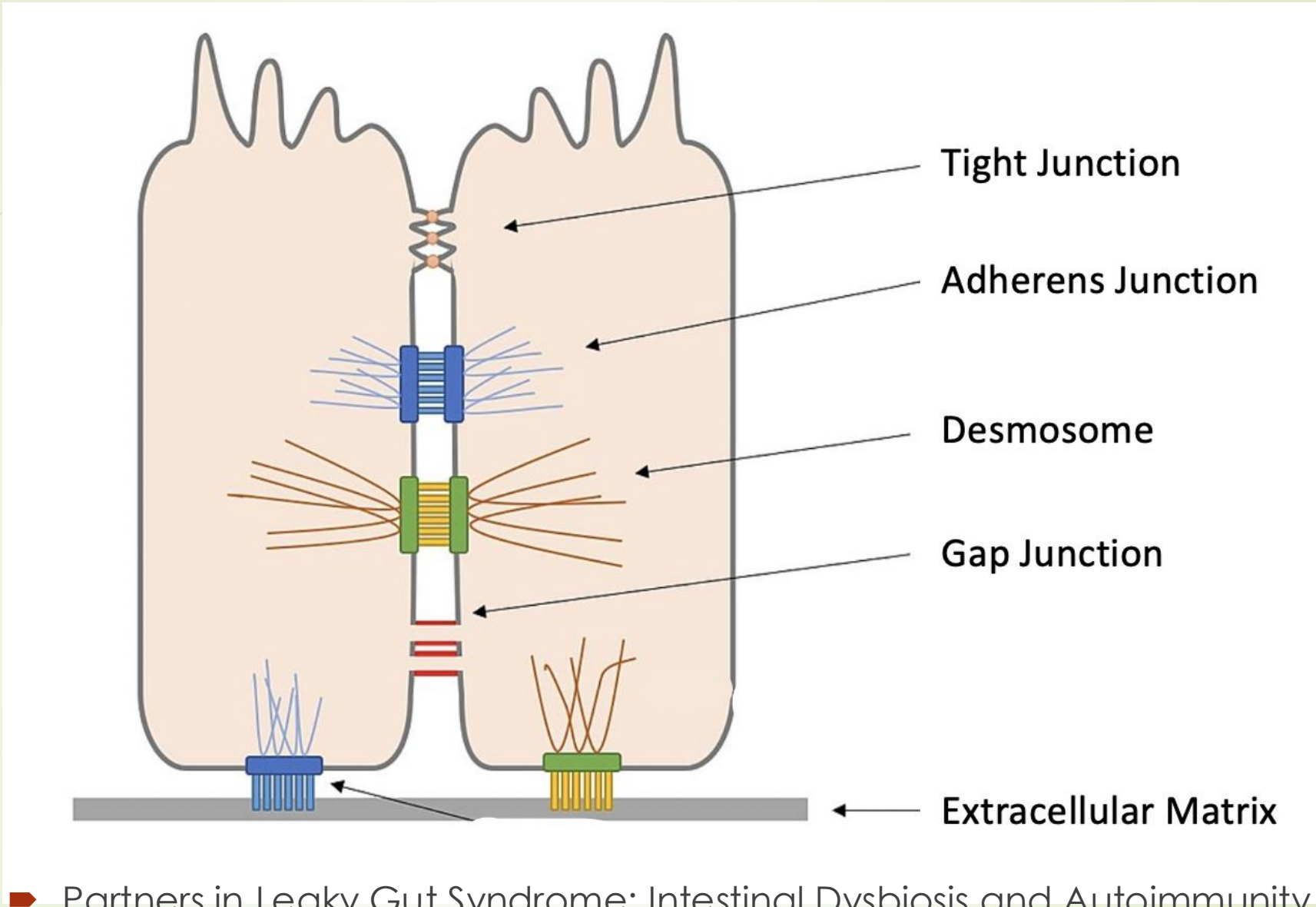
- **What do we do with a diagnosis?**
  - Work on the joints mostly affected.
  - Work on the patient's main concerns
- **What does managing mean.**
  - Work on the connective system first
  - Followed by associations/comorbidities
- **Basics of clinical care.**
  - Listen to and believe the patient.



Lombard et al., 2002, University of Michigan, 2018).



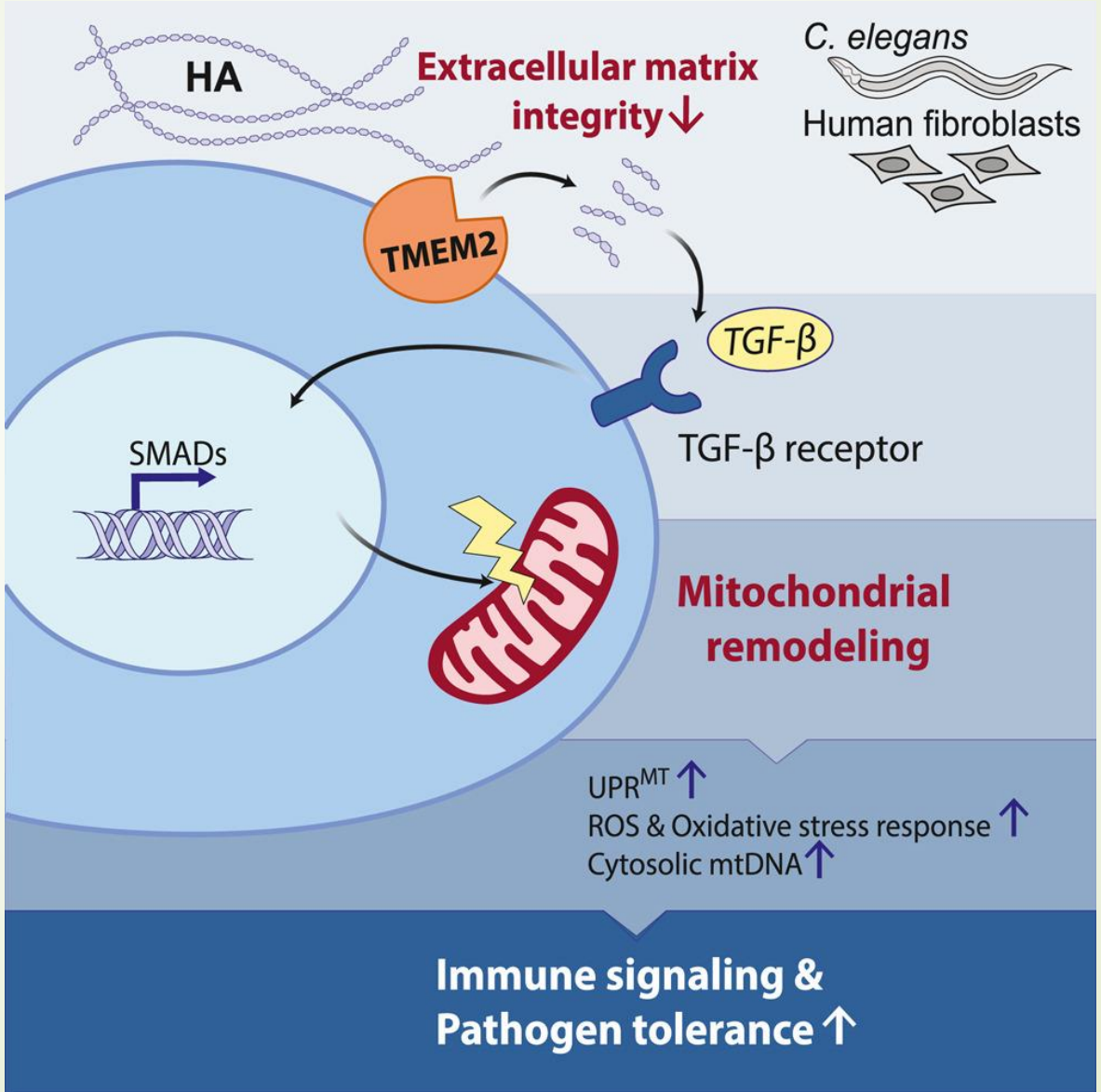
Immunological response to gluten peptides (EscuderoHernández et al., 2016).



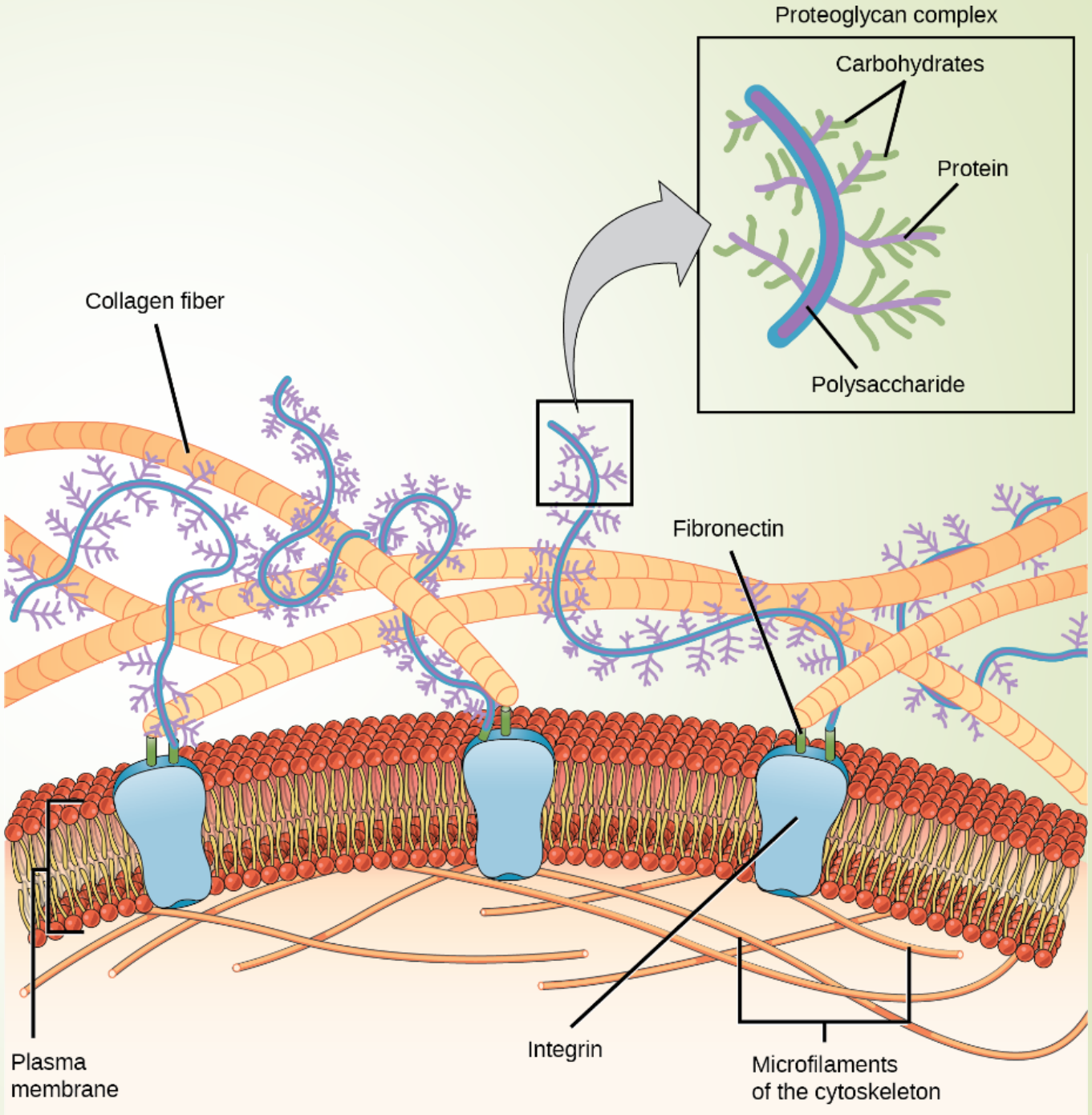
- Partners in Leaky Gut Syndrome: Intestinal Dysbiosis and Autoimmunity

Frontiers in Immunology | www.frontiersin.org 1 April 2021 | Volume 12 | Article 673708

A recent study by Zhang et al. (2024) published in Cell explores a novel connection between the extracellular matrix (ECM) and mitochondrial function. The research demonstrates that ECM remodeling influences mitochondrial homeostasis through an evolutionarily conserved signaling pathway, involving TGF-β activation and mitochondrial stress responses



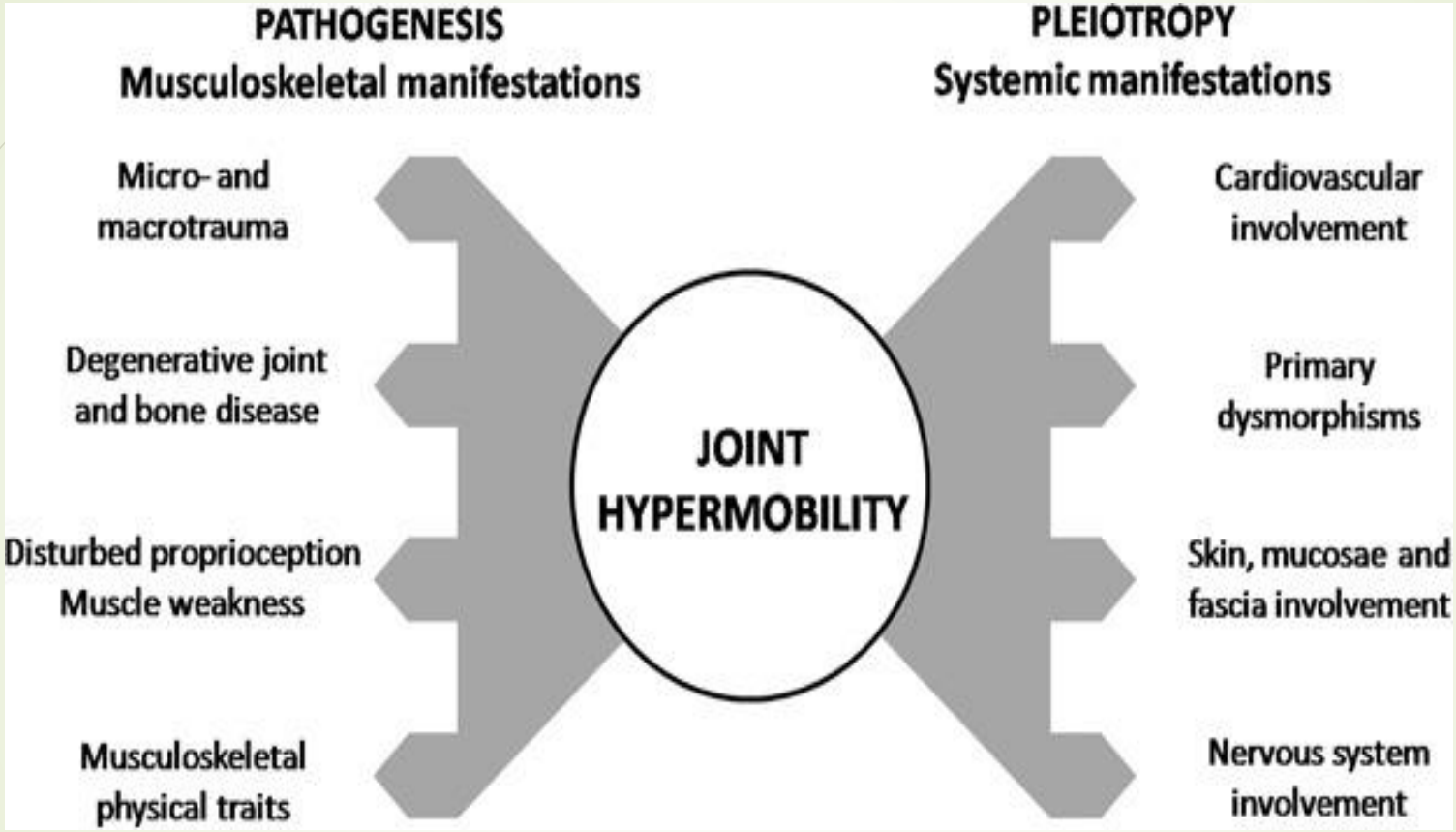
In the human body, cell fate, function, and survival are determined by the microenvironment, a rich and complex network composed of extracellular matrix (ECM), different cell types, and soluble factors. They all interconnect and communicate, receiving and sending signals, modulating and responding to cues.



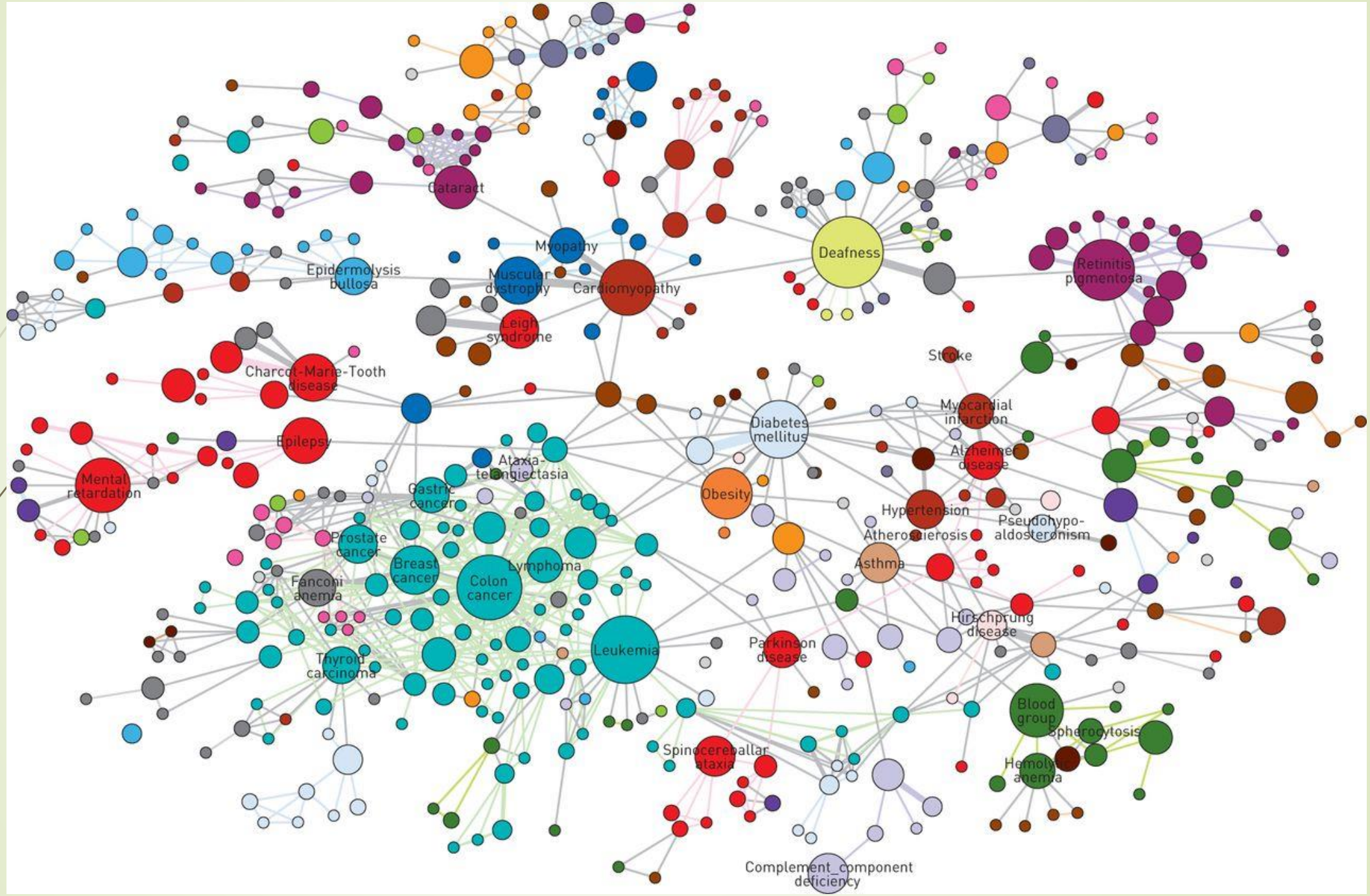
SOME GENETIC TERMS

- **Penetrance:** has a condition by a certain age or not.
- **Variable expression:** if penetrant, variable expression of that condition throughout life.
- **Pleiotropy** is the biological mechanism underlying genetic syndromes, that is, patterns of anomalies each caused directly by a defective gene simultaneously (and independently) affecting the development/functions of different tissues/organs/structures. Eg. Sickle cell anemia

A framework for the classification of joint hypermobility and related conditions



American J of Med Genetics Pt C, Volume: 175, Issue: 1, Pages: 148-157, First published: 01 February 2017, DOI: (10.1002/ajmg.c.31539)


Cataract
Myopathy
Epidermolysis bullosa
Muscular dystrophy
Cardiomyopathy
Deafness
Retinitis pigmentosa
Leigh syndrome
Charcot-Marie-Tooth disease
Stroke
Myocardial infarction
Diabetes mellitus
Epilepsy
Alzheimer disease
Ataxia-telangiectasia
Mental retardation
Gastric cancer
Obesity
Hypertension
Pseudohypo-aldosteronism
Atherosclerosis
Prostate cancer
Asthma
Breast cancer
Lymphoma
Colon cancer
Fanconi anemia
Hirschprung disease
Leukemia
Parkinson disease
Thyroid carcinoma
Blood group
Spherocytosis
Spinocerebellar ataxia
Hemolytic anemia
Complement_component deficiency

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Please visit www.eeds.com and sign into this event by scanning the QR code or enter the following activity code:

06DAUB (valid until Friday 5/22, 6:30 PM)

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