

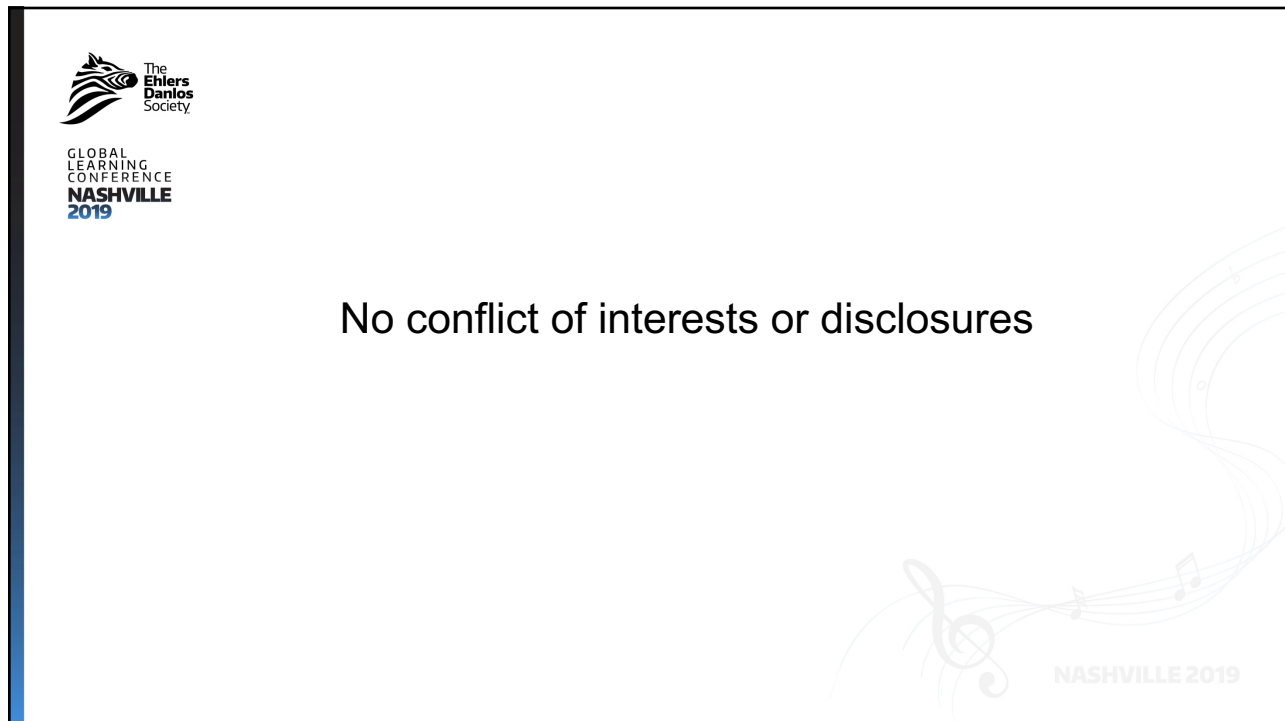
The slide features a white rectangular frame containing the Ehlers-Danlos Society logo on the left, which consists of a stylized zebra head profile. To the right of the logo is a vertical blue line. Further right, the title "The Skin in the Ehlers-Danlos Syndromes" is written in a large, bold, blue font. Below the title, the speaker's name and affiliation are listed in a smaller black font. At the bottom center of the frame, the text "GLOBAL LEARNING CONFERENCE NASHVILLE 2019" is displayed, with "NASHVILLE 2019" in a larger, bold, blue font.

The Ehlers Danlos Society

The Skin in the Ehlers-Danlos Syndromes

Dr Nigel Burrows
Consultant Dermatologist MD FRCP
Department of Dermatology
Addenbrooke's Hospital Cambridge University NHS Foundation Trust
Cambridge, UK

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This slide contains the Ehlers-Danlos Society logo in the top left corner and the "GLOBAL LEARNING CONFERENCE NASHVILLE 2019" logo below it. The main text "No conflict of interests or disclosures" is centered on the slide in a black font. In the bottom right corner, there is a decorative graphic of a treble clef and musical notes, with the text "NASHVILLE 2019" positioned below it.

The Ehlers Danlos Society

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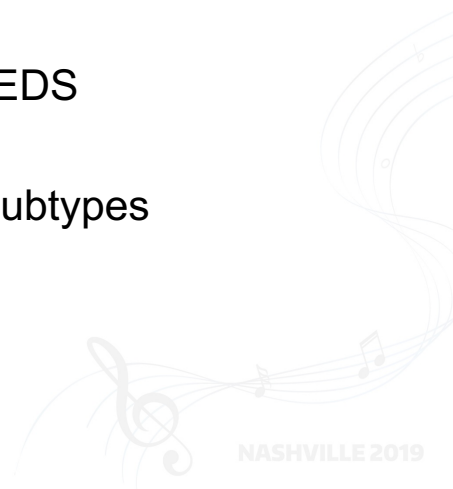
No conflict of interests or disclosures

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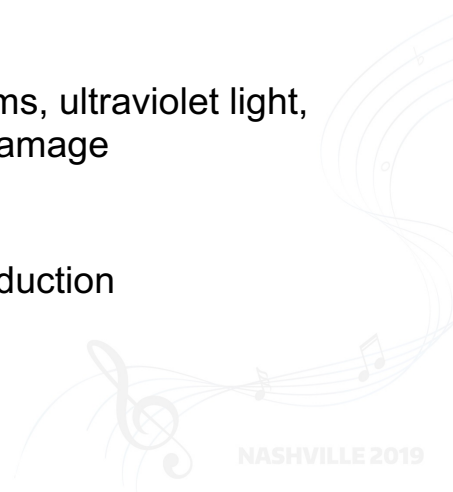
- Overview of skin and anatomy
- Skin features in commoner EDS
- Skin features in rarer EDS subtypes
- Skin management



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The skin

- Is useful organ to sustain life
 - **Protection** - microorganisms, ultraviolet light, mechanical damage
 - **Sensation**
 - **Allows movement**
 - **Endocrine** - vitamin D production
 - **Excretion** - sweat
 - **Temperature regulation**





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The skin

- Is useful organ to sustain life
- Provides a visual clue to diagnoses
- Important for cultures and traditions
- Ready material for research



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Skin Fun Facts

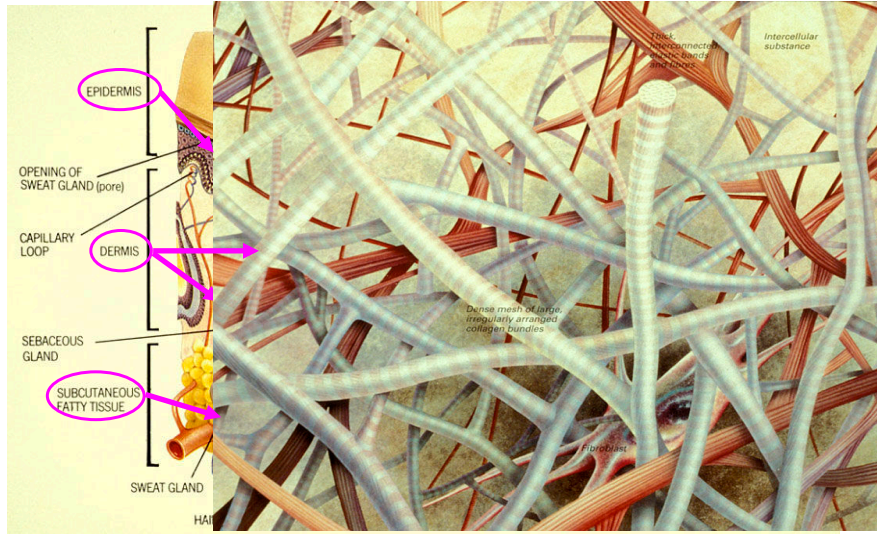
- Largest organ in the body
- In an average adult the skin weighs approx 5kg (11lbs) and covers 2m² (21 sq ft)
- 11 miles of blood vessels
- The average person has about 300 million **skin** cells
- More than half of the dust in your home is actually dead skin
- Your skin is home to more than 1,000 species of bacteria

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The skin has 3 main layers



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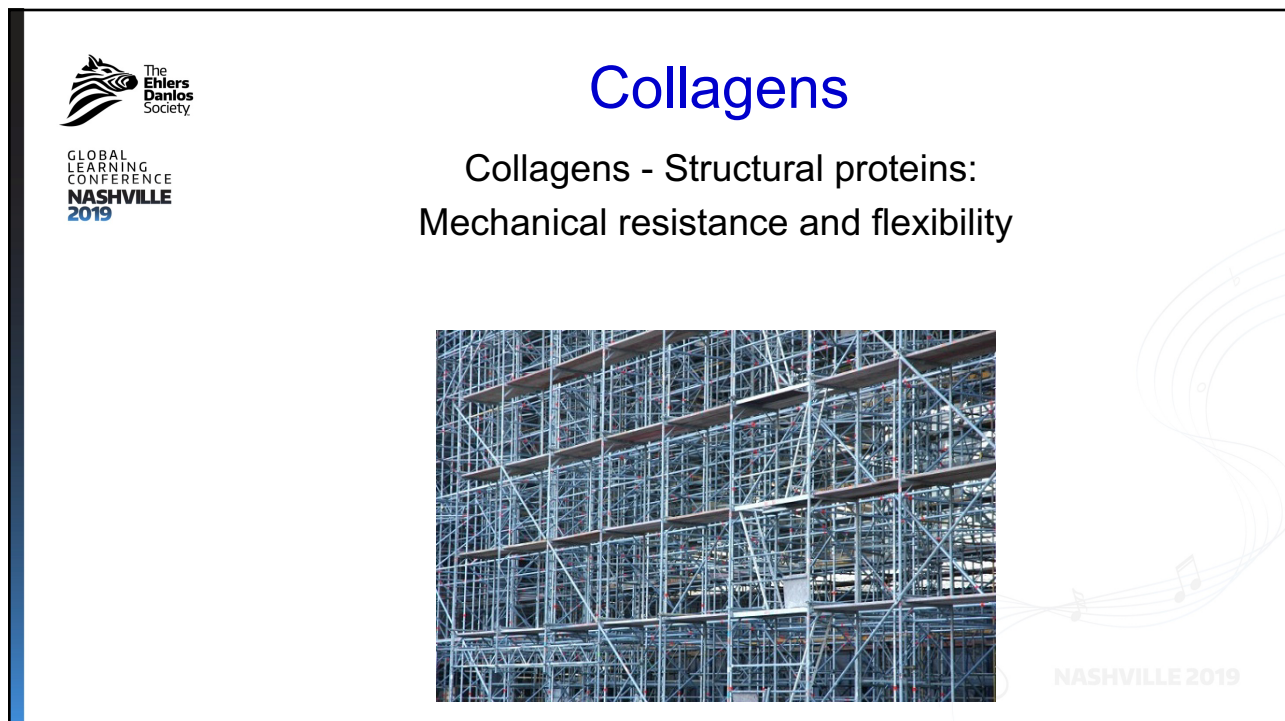
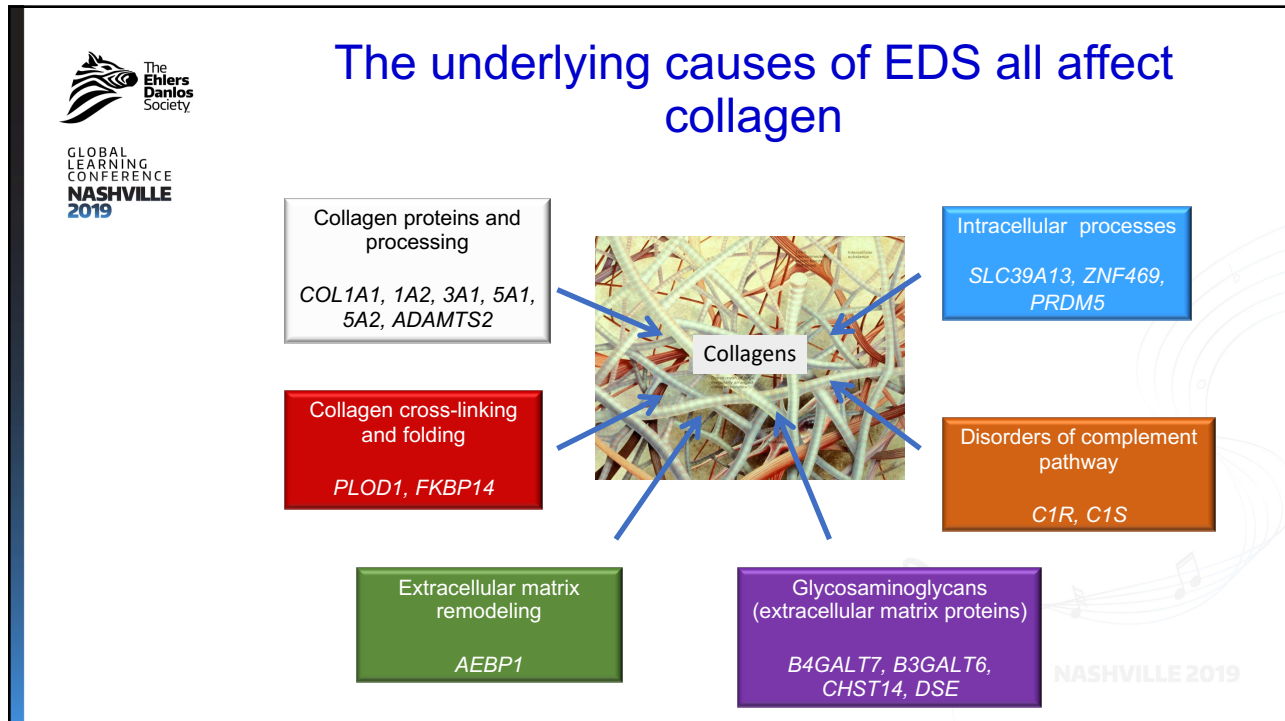
Within the Dermis

Extracellular Matrix

1. Collagen
2. Elastic fibres
3. Ground Substances
 - i) glycosaminoglycans,
 - ii) proteoglycans,
 - iii) glycoproteins and
 - iv) other extra-fibrillar matrix



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Skin Changes in EDS



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| EDS subtype | Skin Related Clinical Features |
|--------------------------------|--|
| Classical | Soft, velvety, doughy, and hyperextensible skin; thin (atrophic) scars, especially over bony protuberances; easy bruising. |
| Classical-like | Similar to mild classical type but normal scarring. |
| Cardiac-valvular | Similar to classical type |
| Vascular | Thin, translucent skin, scarring and very easy bruising |
| Hypermobile | Less pronounced skin changes |
| Arthrochalasia | Hyperextensible and fragile skin with atrophic scars, easy bruising |
| Dermatosparaxis | Severe skin fragility, with redundant sagging skin, soft and doughy, easy bruising, |
| Kyphoscoliotic | Hyperextensible skin, easy bruising, skin fragility with atrophic scars, follicular keratosis |
| Brittle cornea syndrome | Soft, velvety skin, translucent skin |
| Spondylodysplastic | Hyperextensible, thin translucent skin, soft and doughy. Single transverse palmar crease |
| Musculocontractural | Hyperextensible and fragile skin with atrophic scars, easy bruising, wrinkled palms |
| Myopathic | Soft, doughy skin with atrophic scars |
| Periodontal | Pretibial hyperpigmented plaques, easy bruising, fragile skin with atrophic scars |

The 2017 International Classification of the Ehlers–Danlos Syndromes





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Diagnostic Criteria of classical EDS (cEDS)

Major criteria

1. Skin hyperextensibility and atrophic scarring
2. Generalized joint hypermobility

Minor criteria

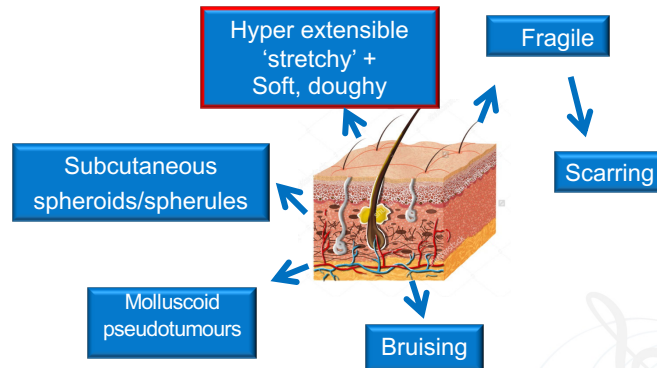
1. Easy bruising
2. Soft, doughy skin
3. Skin fragility (or traumatic splitting)
4. Molluscoid pseudotumours
5. Subcutaneous spheroids
6. Hernia
7. Epicanthal folds
8. Complications of joint hypermobility(e.g., sprains, luxation/subluxation, pain)
9. Family history of a first degree relative who meets clinical criteria


American Journal of Medical Genetics Part C (Seminars in Medical Genetics) 175C:8-26 (2017)



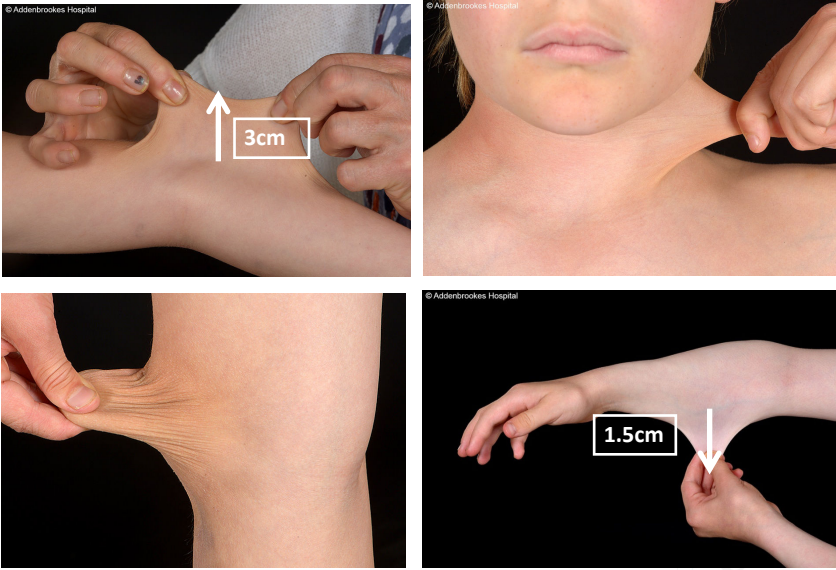
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Skin Changes





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Cutaneous Hyperextensibility

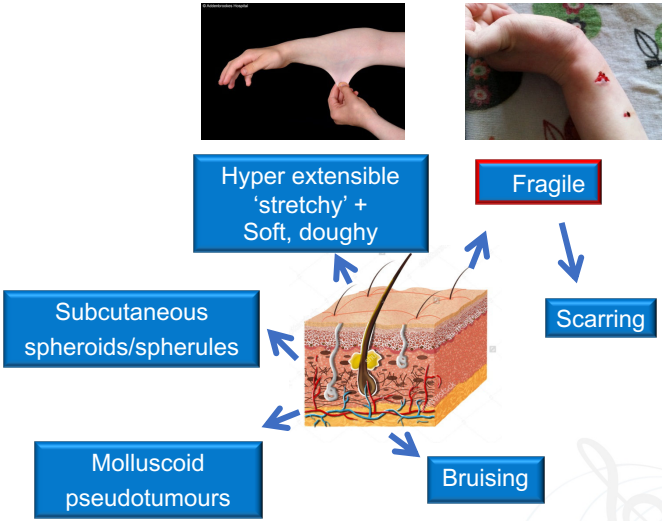


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Skin Changes



Hyper extensible 'stretchy' + Soft, doughy

Fragile

Scarring

Bruising

Molluscoid pseudotumours

Subcutaneous spheroids/spherules


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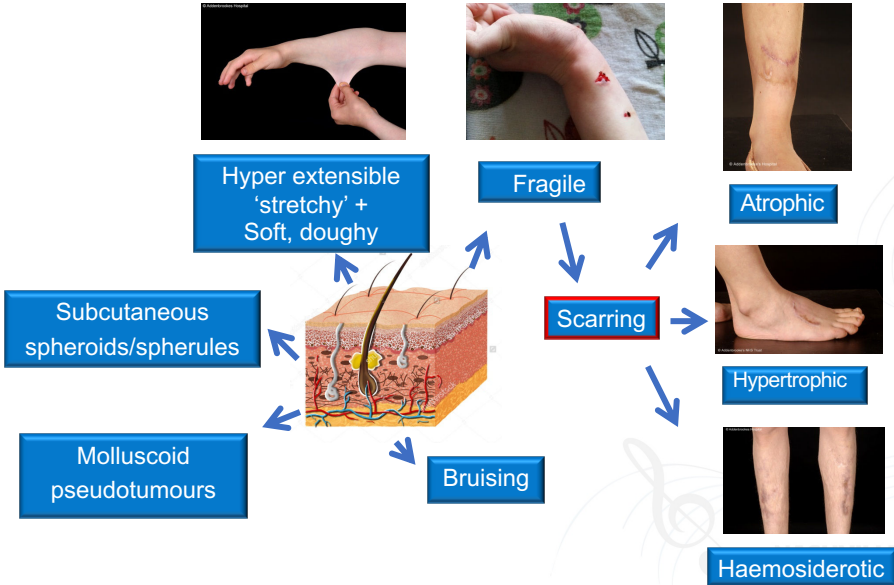
Skin Fragility



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Skin Changes



Hyper extensible 'stretchy' + Soft, doughy

Subcutaneous spheroids/spherules

Molluscoid pseudotumours

Bruising

Fragile

Scarring

Atrophic

Hypertrophic

Haemosiderotic

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Scarring

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Scarring

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Scarring




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Scarring - types



Atrophic = Thin

Hypertrophic = Thick

Haemosiderotic = bruise like

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Hypermobile EDS **Classical EDS**

American Journal of Medical Genetics Part C (Seminars in Medical Genetics) 175C:8-26 (2017)

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Skin Changes

Hyper extensible 'stretchy' + Soft, doughy

Fragile

Atrophic

Scarring

Hypertrophic

Haemosiderotic

Bruising

Molluscoid pseudotumours

Subcutaneous spheroids/spherules

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 **Bruising**

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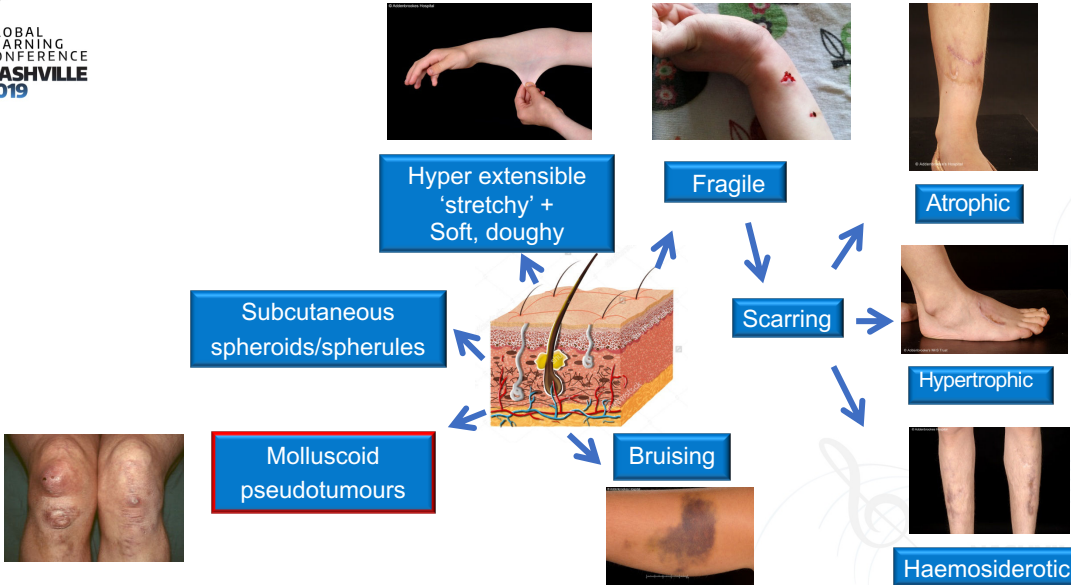


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 **Skin Changes**

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Hyper extensible 'stretchy' + Soft, doughy

Fragile

Atrophic

Scarring

Hypertrophic


Bruising

Haemosiderotic

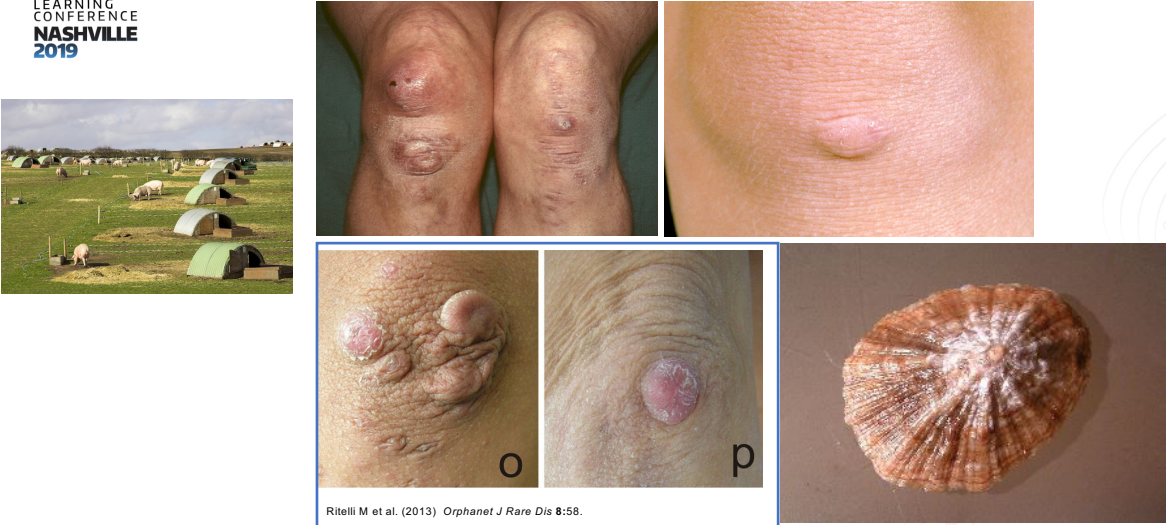
Molluscoid pseudotumours

Subcutaneous spheroids/spherules


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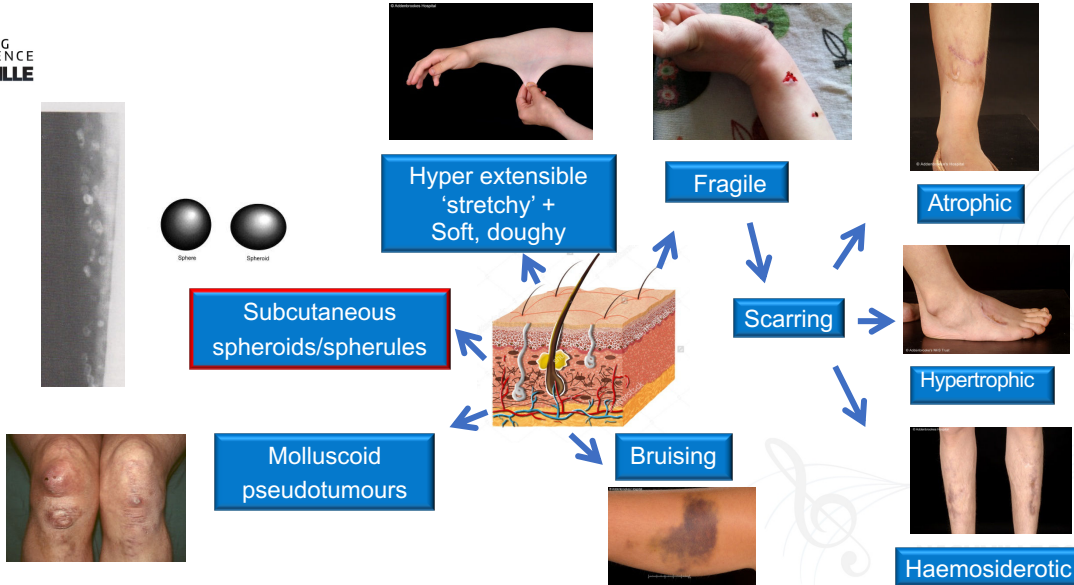
Molluscid pseudotumours



Ritelli M et al. (2013) *Orphanet J Rare Dis* 8:58.


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Skin Changes



Hyper extensible 'stretchy' + Soft, doughy

Fragile

Atrophic


Scarring

Hypertrophic

Haemosiderotic


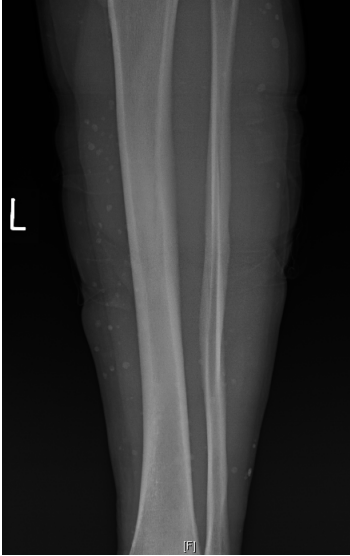
Molluscid pseudotumours

Subcutaneous spheroids/spherules

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Subcutaneous Spheroids

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American Journal of Medical Genetics Part C (Seminars in Medical Genetics) 175C:8-26 (2017)

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Additional Skin Changes

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Lax skin



3yr old with cEDS



Ritelli et al 2013

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Additional Skin Changes – around eyes



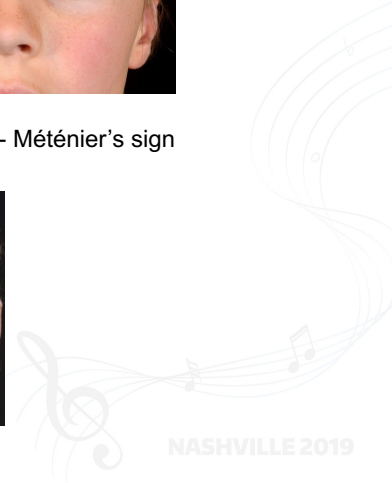
Epicanthic folds



Floppy eyelids - Méténier's sign



Loose eyelid skin



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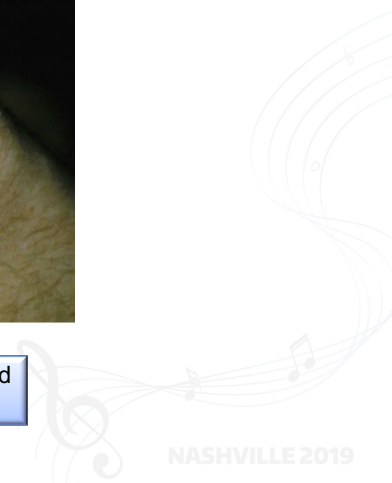


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Additional skin changes



Follicular prominence over elbows and knees



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Additional skin changes



Elastosis perforans serpiginosa

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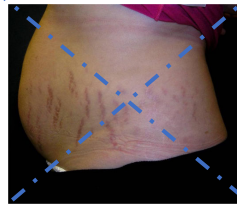
Striae (stretch marks)

Striae 3/40 patients with
cEDS - *Ritelli et al 2013*

7.5%

11/62 patients with cEDS
Columbi et al 2017

18%



hEDS: Diagnostic criteria
Unexplained stretch marks - back, groins,
thighs, breasts and/or abdomen in
adolescents, men or prepubertal women
without a history of significant gain or loss
of body fat or weight



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Other features of tissue weakness



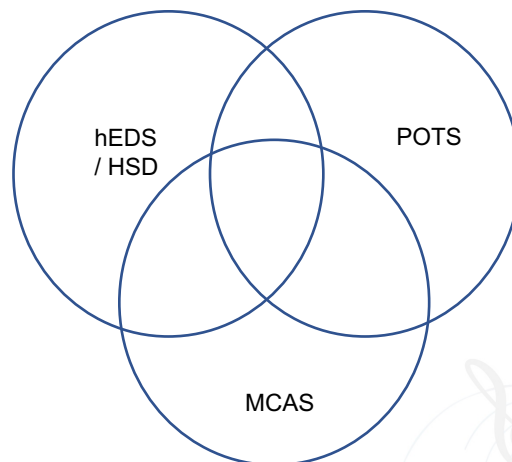
Piezogenic papules

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Hypermobile EDS/Hypermobility Spectrum Disorder



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Mast Cell Activation Syndrome

- **Heart related symptoms:**
rapid pulse (tachycardia), low blood pressure (hypotension) and passing out (syncope).
- **Skin related symptoms:**
itching (pruritus), hives (urticaria), swelling (angioedema) and skin turning red (flushing).
- **Lung related symptoms:**
wheezing, shortness of breath and harsh noise when breathing (stridor) that occurs with throat swelling.
- **Gastrointestinal tract symptoms:**
diarrhoea, nausea with vomiting and crampy abdominal pain.

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hEDS - MCAS




TMS
THE MASTOCYTOSIS SOCIETY
Mast Cell Diseases

Flushing




Urticaria

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Rarer EDS subtypes



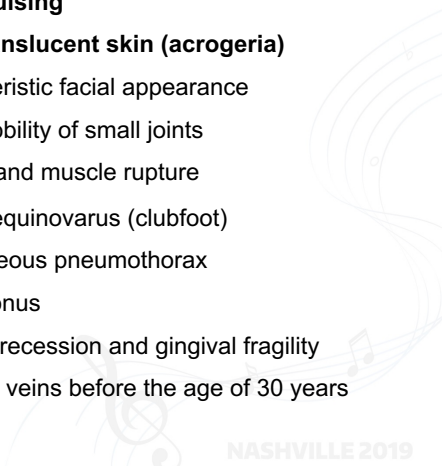
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Vascular EDS (vEDS)

| Major Criteria | Minor Criteria |
|--|---|
| Family history of vEDS (+ COL3A1 mutation) confirmed | Easy bruising |
| Arterial rupture at young age | Thin, translucent skin (acrogeria) |
| Spontaneous sigmoid colon perforation | Characteristic facial appearance |
| Carotid-cavernous fistula | Hypermobility of small joints |
| Uterine rupture | Tendon and muscle rupture |
| | Talipes equinovarus (clubfoot) |
| | Spontaneous pneumothorax |
| | Keratoconus |
| | Gingival recession and gingival fragility |
| | Varicose veins before the age of 30 years |

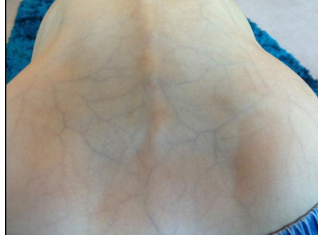


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Translucent Skin



Mother

Daughter

Photographs kindly supplied by patients

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Bruising

- Mother and daughter with vEDS



Photographs kindly supplied by patients

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Periodontal EDS



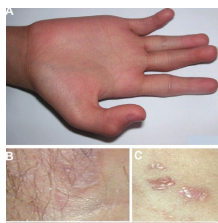
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Very Rare Subtypes of EDS



SpEDS –
SLC39A13



AEPB1-
Related

Ritelli M et al.
Genes 2019;10:135



mcEDS-
CHST14

Brady A et al. Am J Med Genet 175C:70-115 (2017)



Dermatosparaxis

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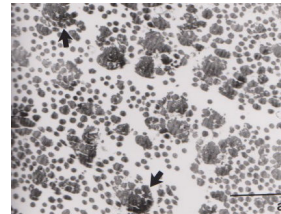
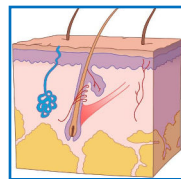
Investigations

- The skin maybe helpful in diagnosis, if there is uncertainty with the genetic testing
- Unfortunately it is not reliable to diagnose hEDS

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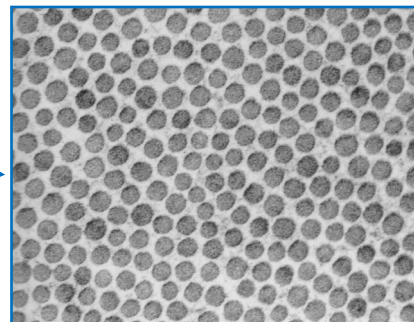


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cEDS

Electron Microscopy



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Skin Management – all the S's



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Skin Management – all the S's

- **Skin protection**

Cover sharp edges of furniture and make homes safe to prevent falls



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Skin Management – all the S's

- Skin protection



"I think we need to take another look at your risk-management strategy."

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Skin Management – all the S's

- Skin protection



- Sport

Consider appropriate sporting activities – avoid contact sports.

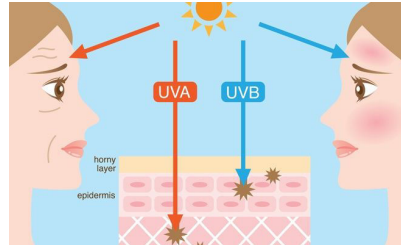




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Skin Management – all the S's

- Skin protection
- Sun avoidance



SPF 50

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Skin Management – all the S's

- Skin protection
- Sun avoidance
- Supplements ?

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| Supplement | Route | Research findings | Outcome | Reference |
|---|-------------------------|---|--|--|
| Retinoids – retinoic acid and retinols | Topically | Increase collagen gene (COL1A1 and CO3A1) expression | Helps wrinkles | Kong R et al. Journal of Cosmetic Dermatology, 2016;15, 49--57 |
| Vitamin B complexes | Tested in cell cultures | positive effect, especially of combinations of B-complex vitamins, on keratinocyte proliferation and fibroblast migration, both of which foster wound healing | Local vitamin application could possibly benefit the physiologic wound healing process | Rembe JD et al. Adve Skin Wound Care 2018;31:225Y33 |
| Vitamin C | Topically | Most studies have found few benefits associated with vitamin C | May possibly slow sun-related skin aging | Pullar JM et al. Nutrients. 2017 Aug; 9(8): 866 |
| | Oral | | Reverses bruising if deficient ie scurvy <i>Reduced bleeding time in kyphoscoliotic EDS</i> | Dempure PP et al. Metabolism 1987;36:687-91 |
| Vitamin E | Oral | | May slow skin aging, but the research is not conclusive | Zussman J et al. J Am Acad Dermatol. 2010 Sep;63(3):507-25 |
| | Topical | | Inconclusive for helping scars | |
| Collagen | oral | No evidence of benefit | | |



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Skin Management – all the S's

- **Skin protection**
- **Sun avoidance**
- **Supplements**
- **Stop Smoking**



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Skin Management – all the S's

- **S**kin protection
- **S**un avoidance
- **S**upplements
- **S**top Smoking
- **S**teroids – caution with corticosteroids



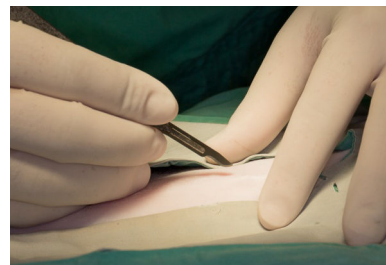
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Skin Management – all the S's

- **S**kin protection
- **S**un avoidance
- **S**upplements
- **S**top Smoking
- **S**teroids
- **S**urgery



Especially for patients with cEDS, vEDS, and kEDS, weigh up the potential benefits of surgery and possible complications of surgery they are planned.

Always consider all non-surgical alternatives.

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Skin Management – all the S's

- **S**kin protection
- **S**un avoidance
- **S**upplements
- **S**top Smoking
- **S**teroids
- **S**urgery
- **S**ticky Adhesives



- If skin very fragile use non adhesive dressings
- Use medical adhesive removers

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Skin Management – all the S's

Minor / Bruises:

- Ice-pack or compression, elevation of the limb

Cuts / Tears less than 1cm length on body:

- Clean wound
- If no tension then wide (6-12mm) steristrips
- +/- glue

Cuts/ Tears that are gaping, jagged or deep:

- Clean wound
- Two layer sutures + steristrips

Facial injuries:

- Suture



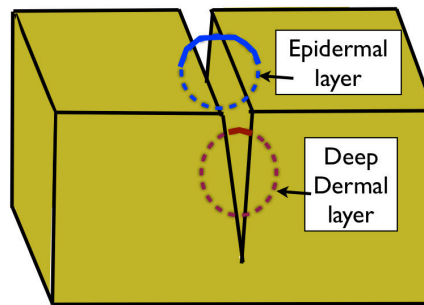
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Skin Management – all the S's

All sutures to stay in twice as long as normal.
Preferably 2 layer suturing



Sterisrips to be applied post suture removal

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Skin Management – all the S's

- Cosmetic procedures such as dermabrasion or skin fillers are probably contraindicated
- Laser treatment carries the risk of thick (hypertrophic) scarring.

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More research required



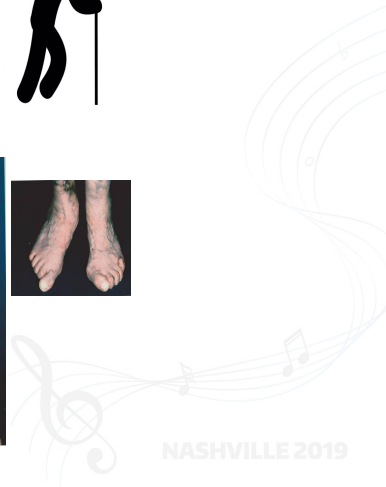
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Natural History?



No prospective studies

Skin – accelerated aged appearance





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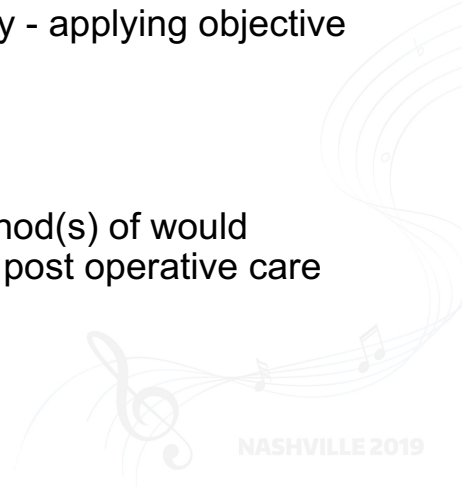
More research required

Diagnostic

- Validation of skin hyperextensibility - applying objective measures

Therapeutic

- Wound Care - to identify best method(s) of wound closure in children and adults and post operative care

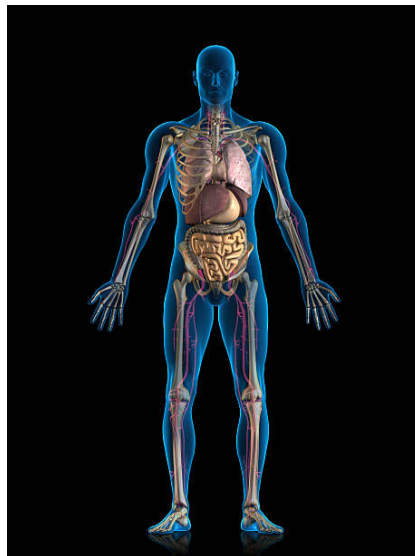


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Don't forget the skin



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en.wikipedia.org

Patients and families with EDS who have kindly given permission to use their clinical photographs.

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