# Phenotypic presentation of Mendelian disease across the diagnostic trajectory in electronic health records

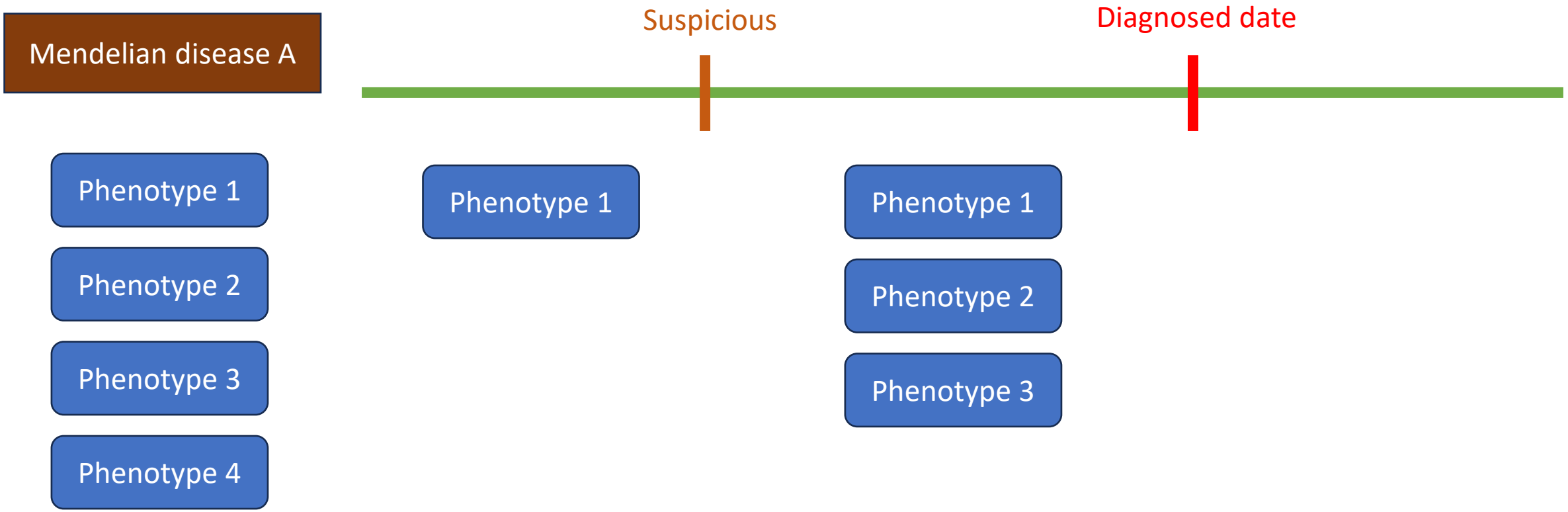
Cholatid R.

# Phenotypic presentation

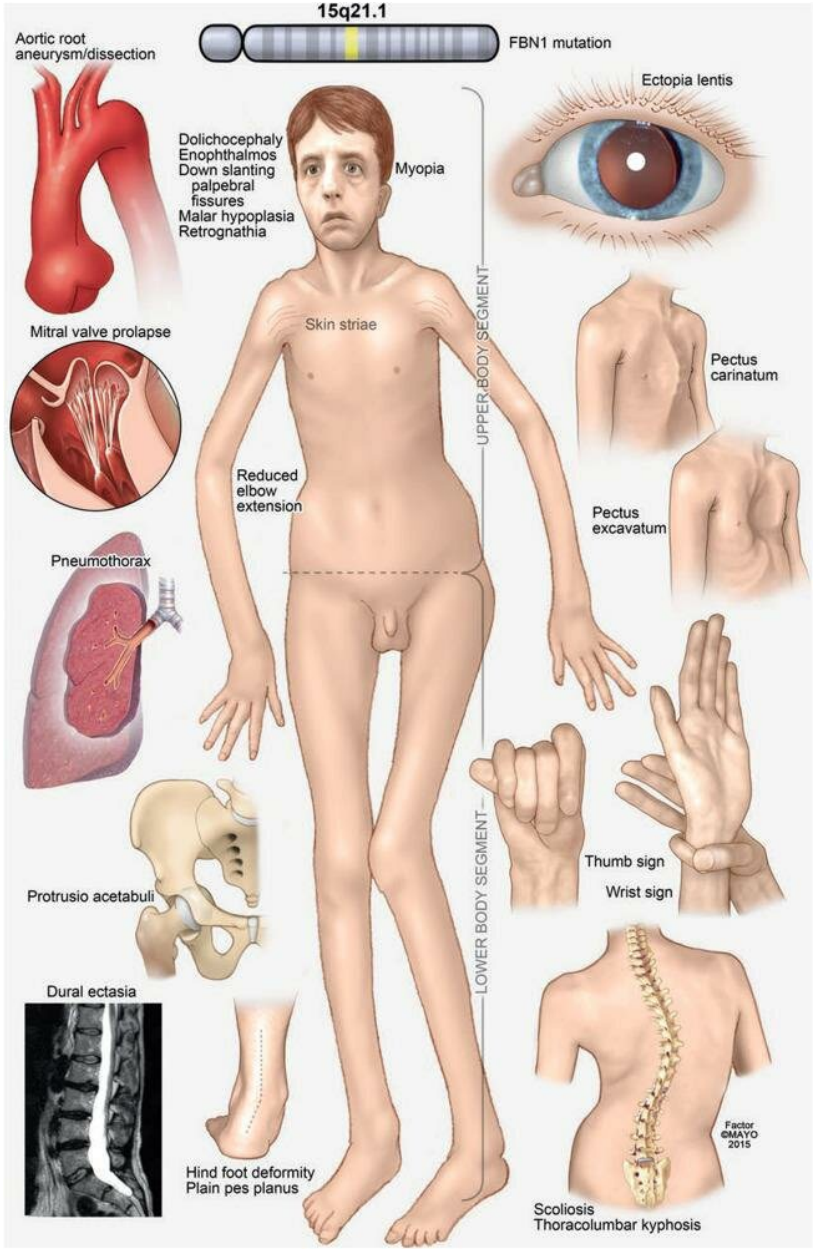
# Phenotype

Is the observation characteristics influenced by genes

# Timeline of a patient

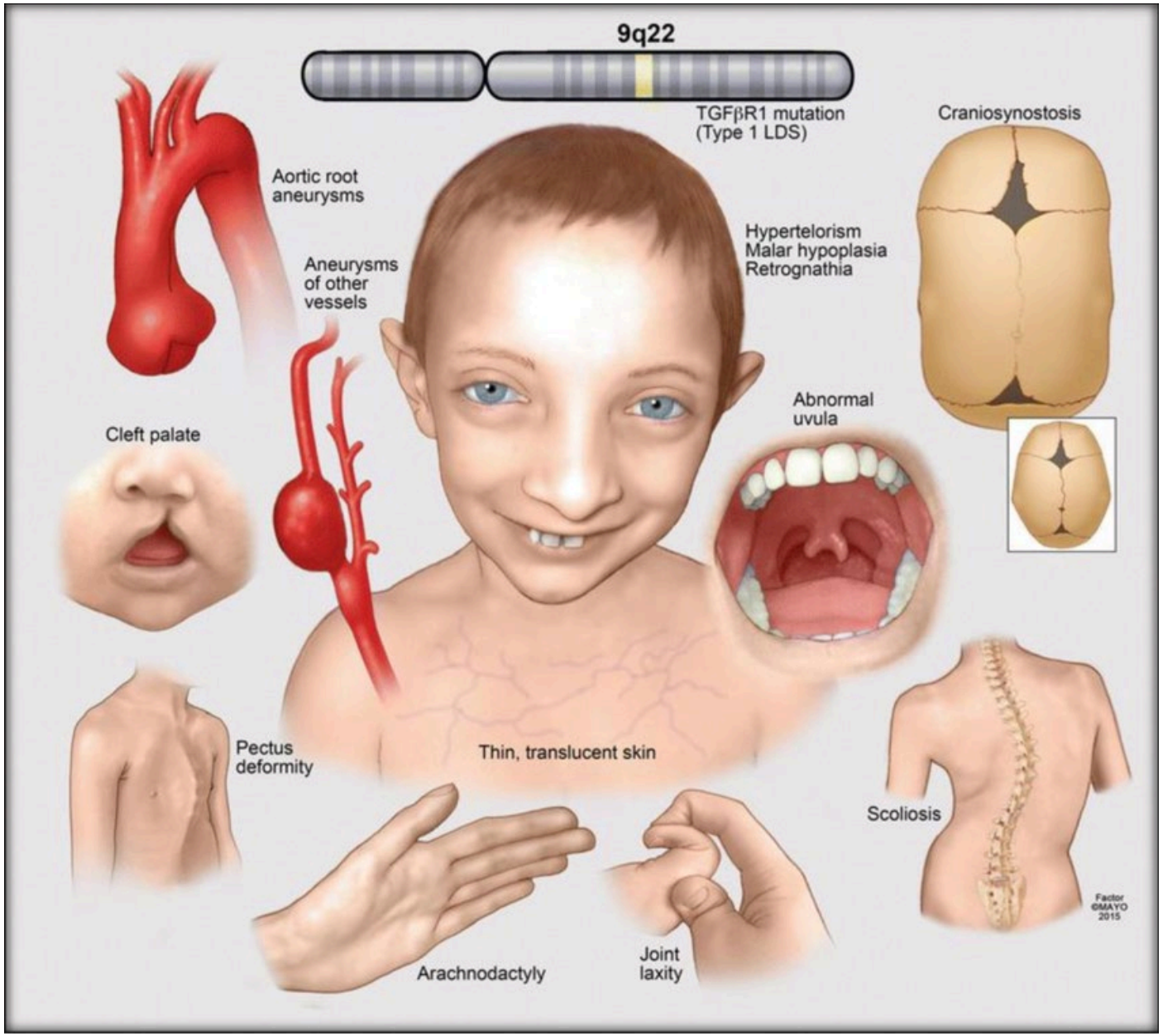


| | |
|---|---|
| Marfan syndrome (MFS) | Connective tissue |
| Loeys-Dietz syndrome (LDS), | Connective tissue |
| Stickler syndrome (STL) | Connective tissue |
| Classical Ehlers Danlos syndrome (cEDS ) | Connective tissue |
| Vascular Ehlers Danlos syndrome (vEDS) | Connective tissue |
| Hereditary Hemorrhagic Telangiectasia (HHT) | Arteriovenous malformations |
| Hypophosphatasia (HPP) | Deficient activity of the tissue-nonspecific isoenzyme of alkaline phosphatase. |
| Noonan syndrome (NS) | Gain of function in cell signaling pathway |
| Adult Cystic fibrosis (aCF) | Abnormal and thick mucus production through the body |



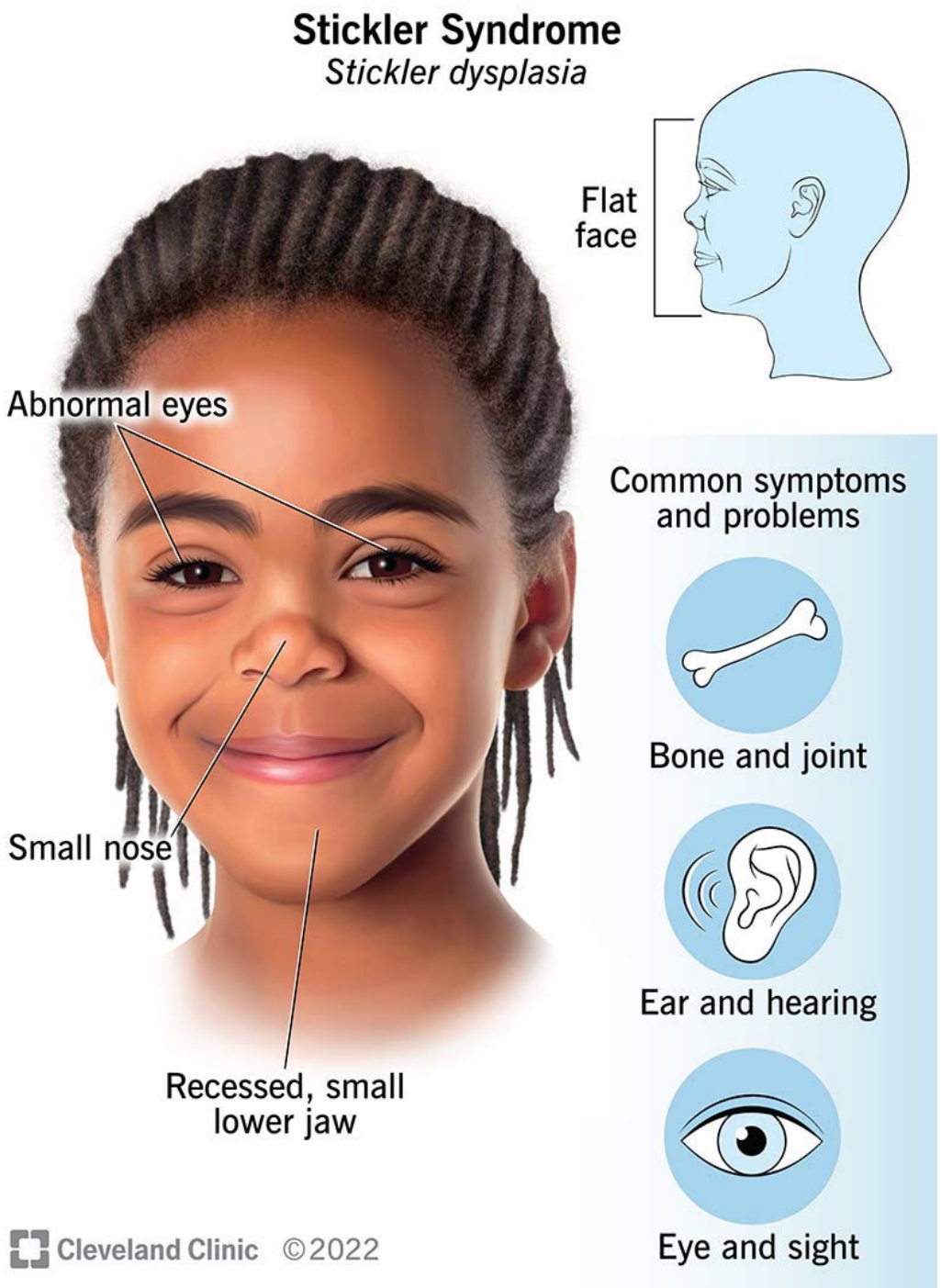

# Marfan syndrome (MFS)

Suleiman, Mathieu. (2023). The Use of Bioelectrical Impedance Analysis as a Contemporary Biomarker in Congenital or Hereditary Diseases with Aortic Involvement.



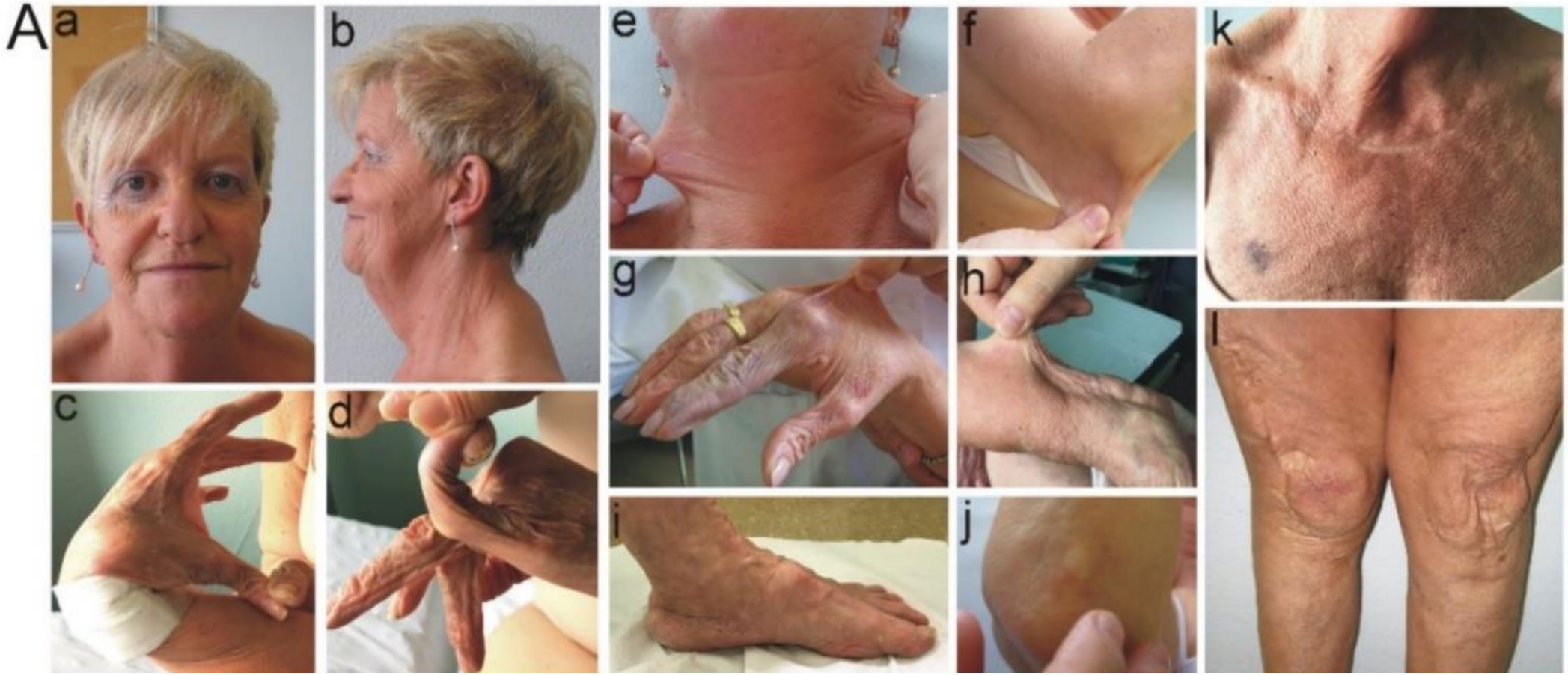

# Loeys-Dietz syndrome

Suleiman, Mathieu. (2023). The Use of Bioelectrical Impedance Analysis as a Contemporary Biomarker in Congenital or Hereditary Diseases with Aortic Involvement.



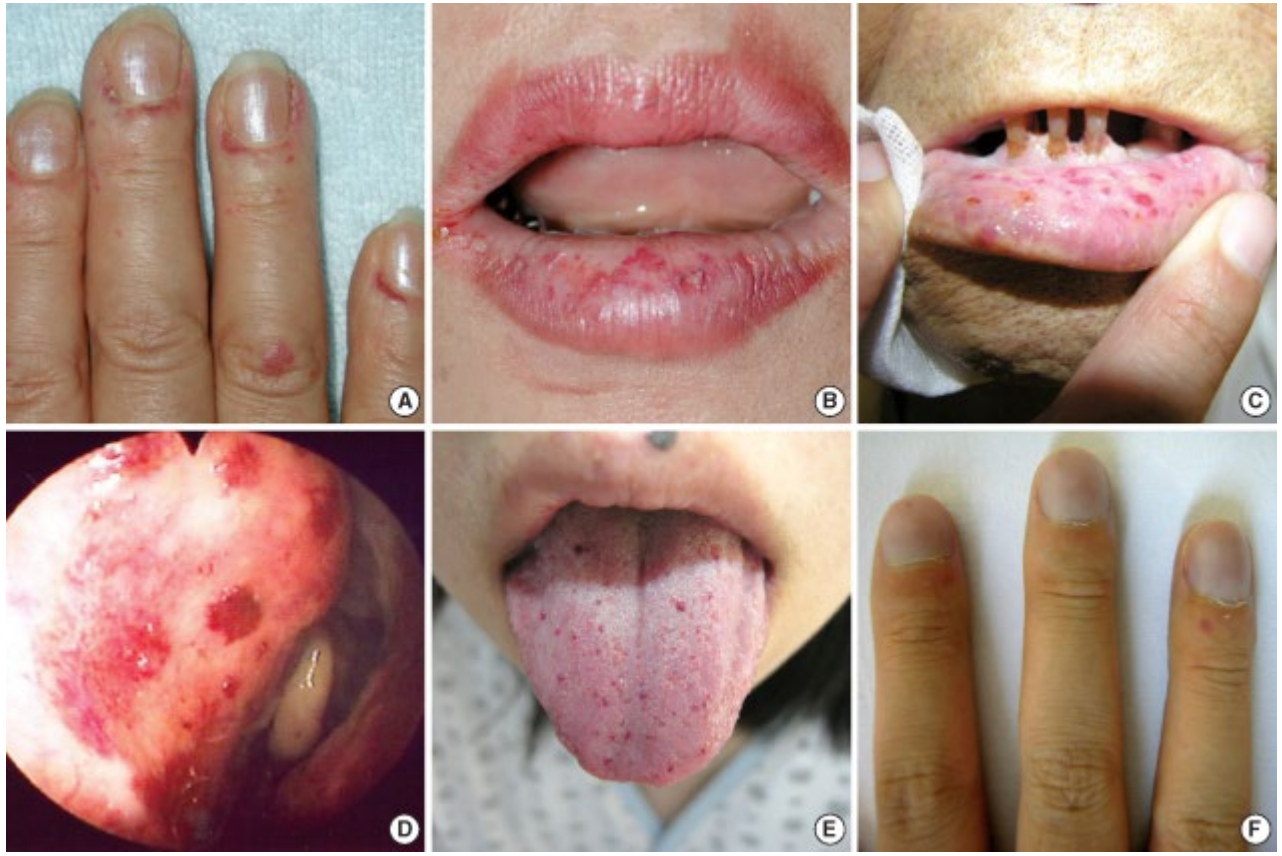

[Stickler Syndrome: Symptoms & Outlook (clevelandclinic.org)]

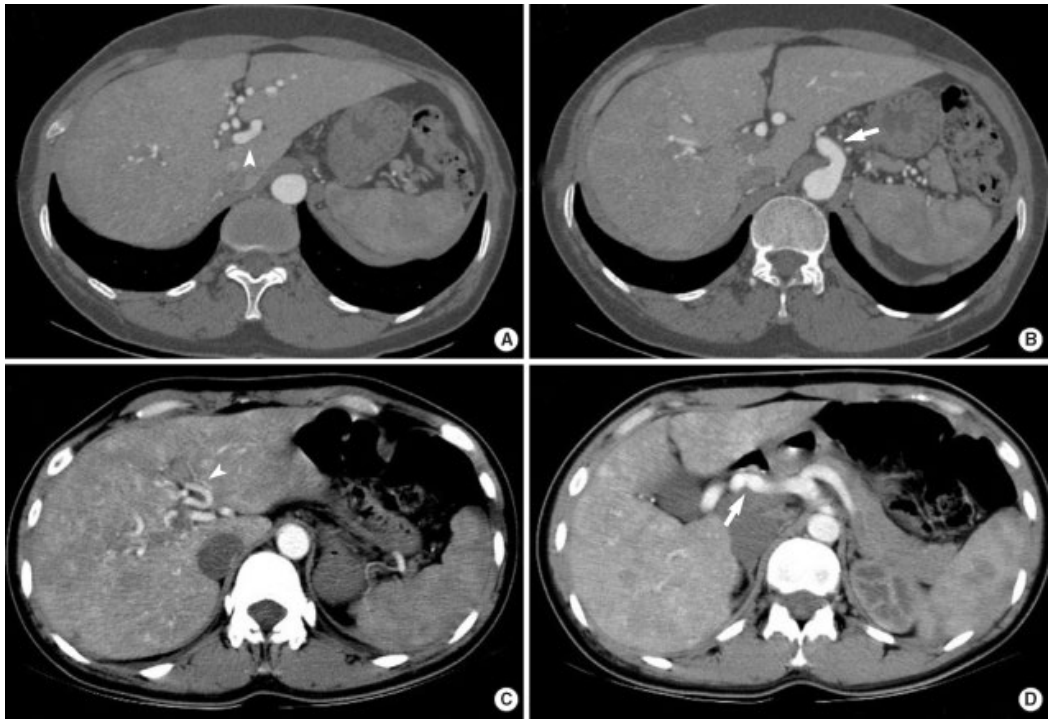
# Classical Ehlers Danlos syndrome (cEDS )




Ritelli M, Cinquina V, Venturini M, Pezzaioli L, Formenti A, Chiarelli N, et al. Expanding the Clinical and Mutational Spectrum of Recessive AEBP1-Related Classical-Like Ehlers-Danlos Syndrome. Genes [Internet] 2019;10(2):135. Available from: http://dx.doi.org/10.3390/genes10020135

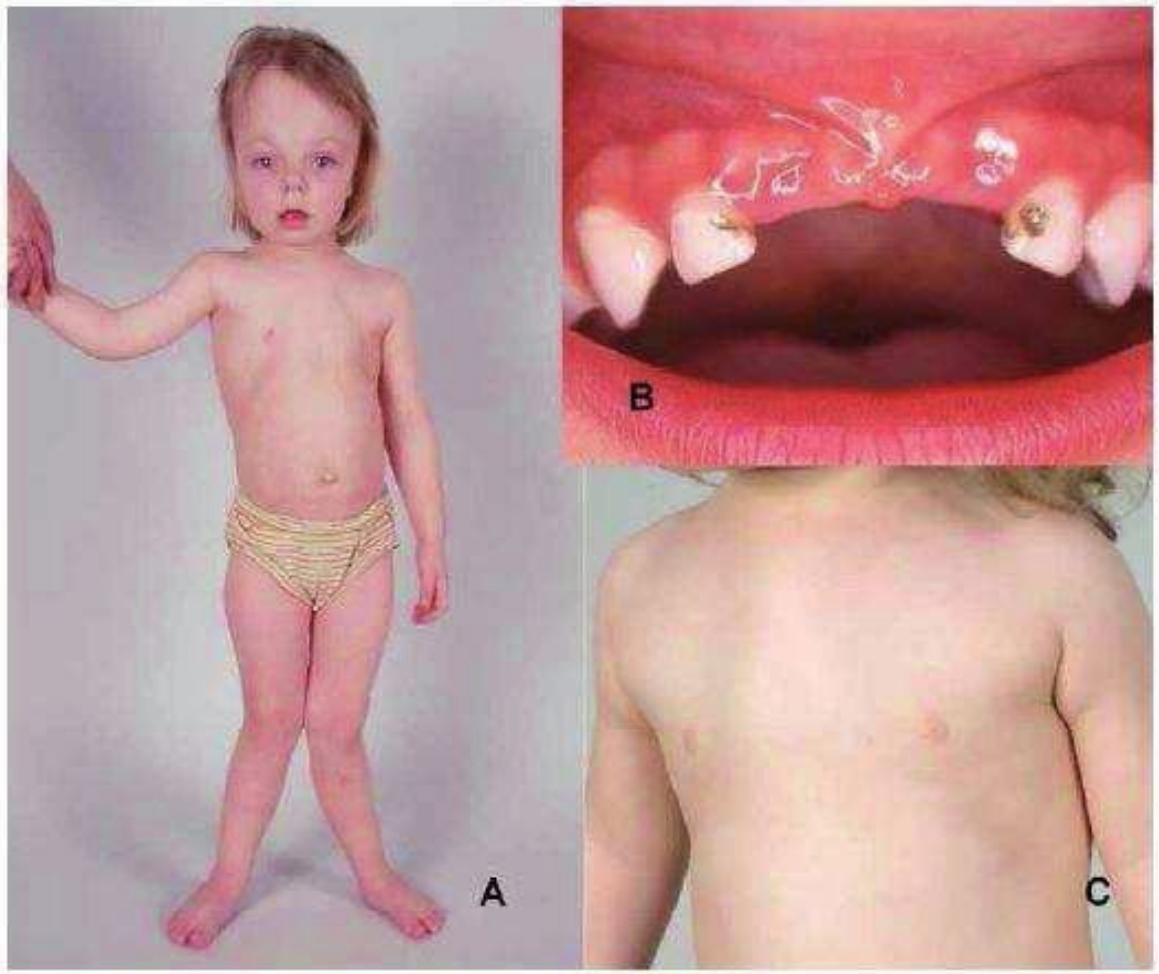
# Hereditary Hemorrhagic Telangiectasia



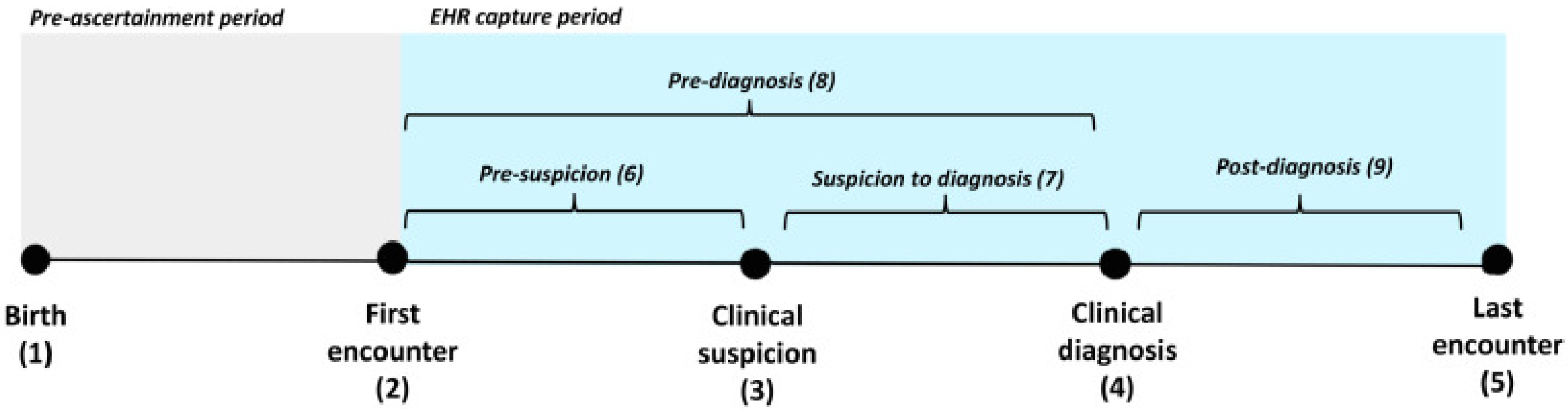

Lee, Seung-Tae & Kim, Jee-Ah & Jang, Shin-Yi & Kim, Duk-Kyung & Do, Young & Suh, Gee Young & Kim, Jong-Won & Ki, Chang-Seok. (2009). Clinical Features and Mutations in the ENG, ACVRL1, and SMAD4 genes in Korean Patients with Hereditary Hemorrhagic Telangiectasia. Journal of Korean medical science. 24. 69-76. 10.3346/jkms.2009.24.1.69.

# Hypophosphatasia




Ehtisham, Mohammad. (2016). CEMENTUM.

# An EHR-based trajectory of the diagnostic process in genetic disease

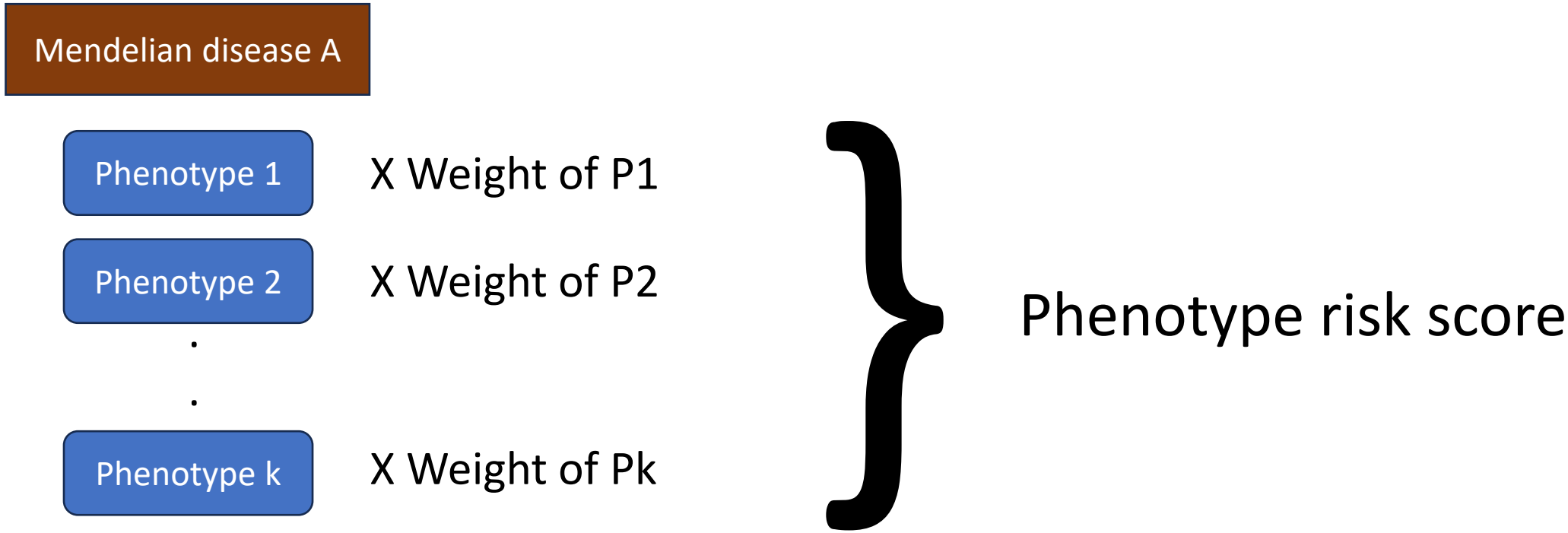


# Cohort data

- Vanderbilt University Medical Center
- at least 3 encounters
- between January 1, 2002, and January 1, 2022
- Control = 1.8 million

| Disease Name | Gene(s) | Abbreviation | Total | Diagnosed Before First Visit *N* (%) | Suspicion On First Encounter *N* (%) | Fully Ascertained Trajectory *N* (%) |
|---|---|---|---|---|---|---|
| Marfan syndrome | *FBN1* | MFS | 145 | 55 (37.9) | 57 (39.3) | 33 (22.8) |
| Ehlers Danlos, Classic | *COL5A1/2* | cEDS | 9 | 2 (22.2) | 1 (11.1) | 6 (66.6) |
| Ehlers Danlos, Vascular | *COL3A1* | vEDS | 27 | 5 (20.8) | 9 (33.3) | 13 (48.1) |
| Loeys-Dietz syndrome | *TGFBR1/2, TGFB2, SMAD2/3* | LDS | 32 | 7 (21.9) | 8 (25.0) | 17 (53.1) |
| Stickler syndrome | *COL2A1, COL11A1, COL9A1, COL9A3* | STL | 40 | 8 (20.0) | 14 (35.0) | 18 (45.0) |
| Hereditary Hemorrhagic Telangiectasia | *ACVRL1, ENG* | HHT | 79 | 28 (35.4) | 19 (24.1) | 32 (40.5) |
| Hypophosphatasia | *ALPL* | HPP | 93 | 53 (57.0) | 10 (10.8) | 30 (32.3) |
| Noonan syndrome | *PTPN11, SOS1, RAF1* | NS | 92 | 17 (18.5) | 26 (28.3) | 49 (53.3) |
| Cystic Fibrosis | *CFTR* | CF | 379 | 353 (93.1) | 7 (1.85) | 18 (4.75) |
| All | — | All | 896 | 528 (60.8) | 151 (16.9) | 216 (24.1) |

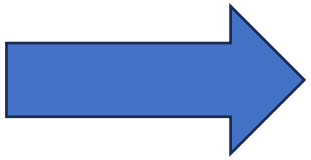
# RESULT




$$\text{Weight} = log_{10}\left(\frac{N}{n_j}\right),$$

$N$ is the total number of individuals in the cohort
$n_j$ is the number of individuals with at least one occurrence of phecode $j$

Phenotype risk score
Sex
Age
Record length

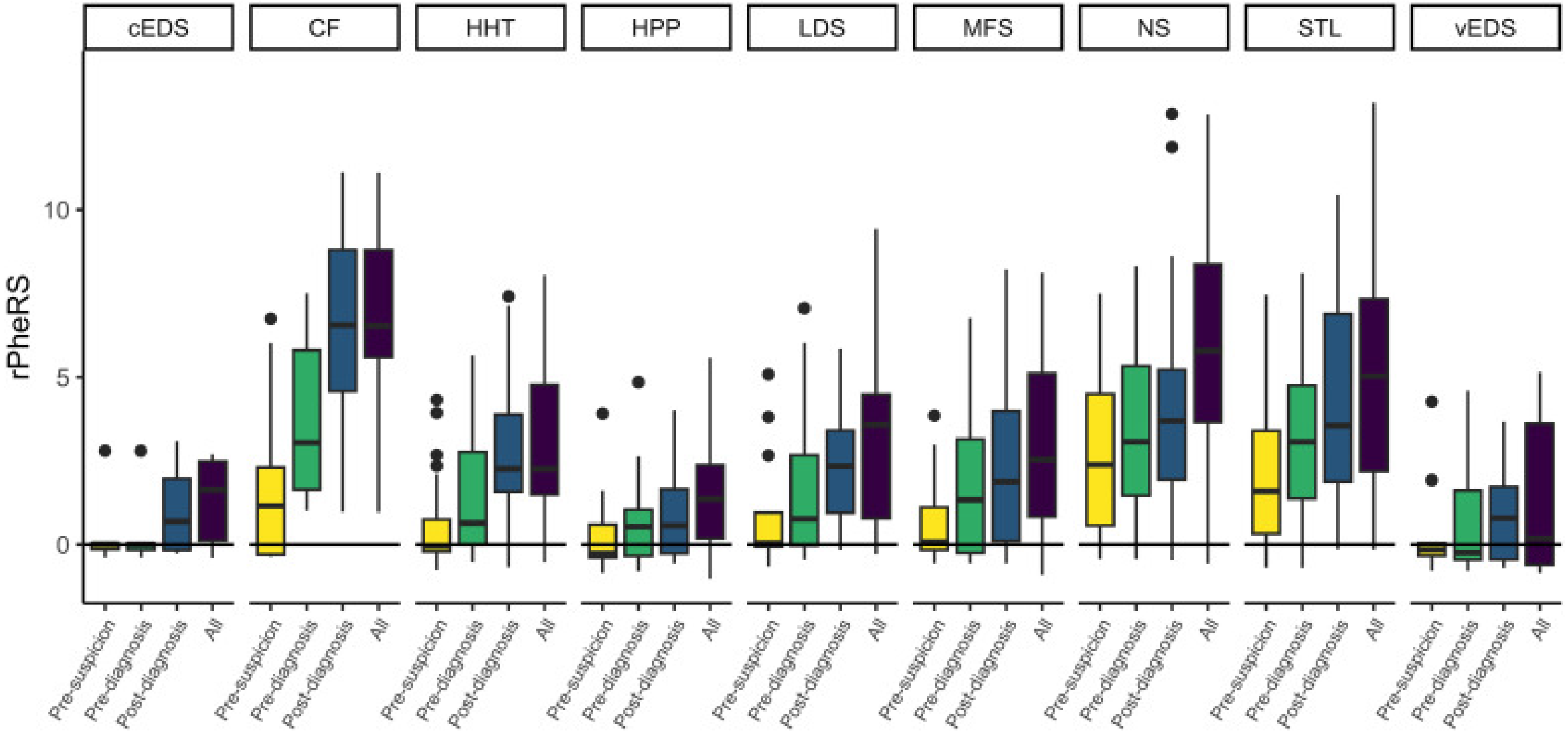


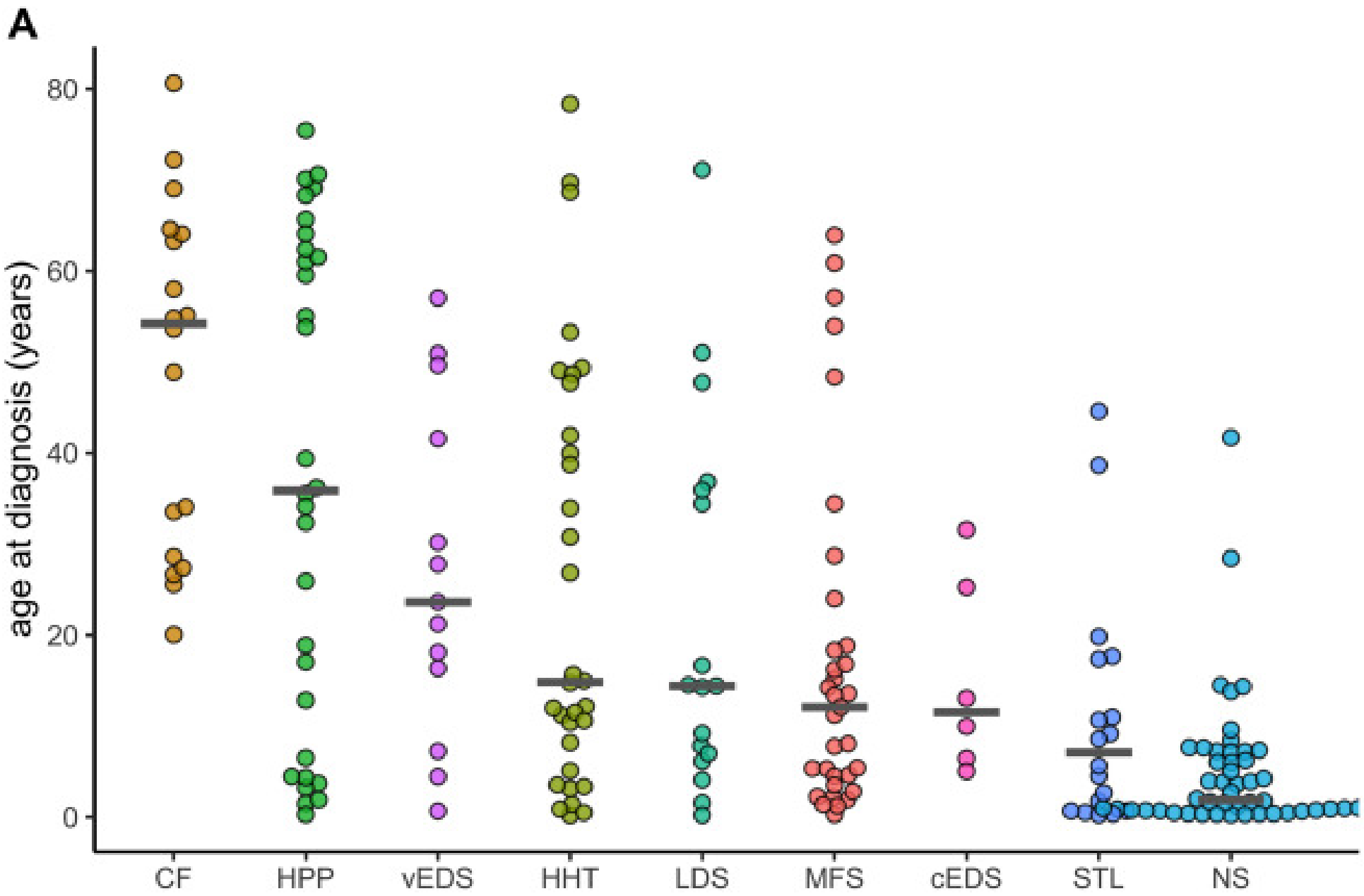
residualized PheRS (rPheRS)

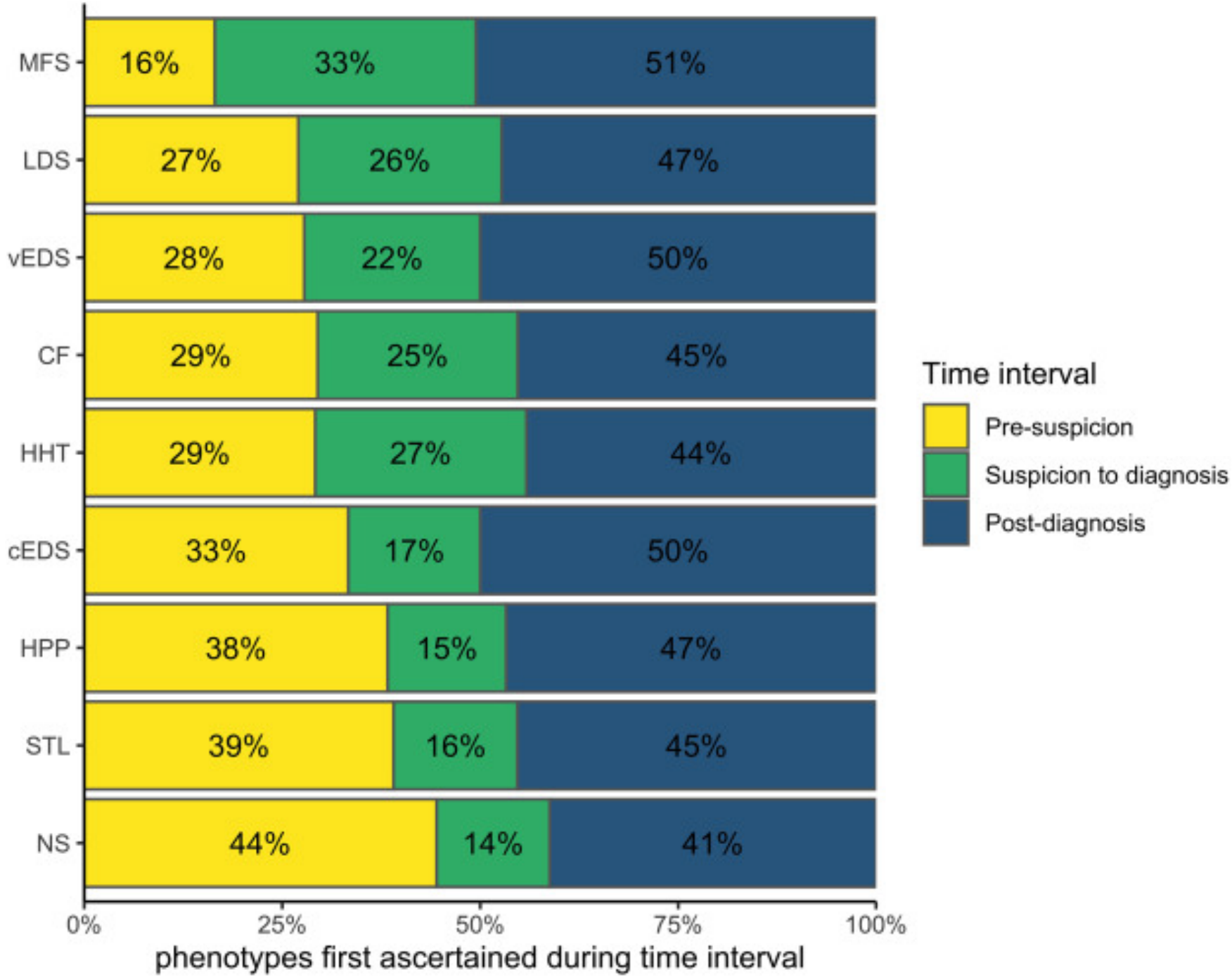
| | Pre-suspicion | | Pre-diagnosis | | Post-diagnosis | | All | |
|---|---|---|---|---|---|---|---|---|
| Disease | Median PheRS | P* | Median PheRS | P* | Median PheRS | P* | Median PheRS | P* |
| MFS | 0.08 [-0.16 - 1.11] | 3.80E-05 | 1.33 [-0.25 - 3.15] | 2.00E-07 | 1.87 [0.11 - 3.98] | 7.10E-12 | 2.54 [0.83 - 5.11] | 1.80E-13 |
| cEDS | 0.01 [-0.14 - 0.03] | 0.043 | 0.00 [-0.16 - 0.03] | 0.05 | 0.70 [-0.17 - 1.97] | 0.015 | 1.64 [0.12 - 2.49] | 0.023 |
| vEDS | -0.16 [-0.33 - 0.04] | 0.192 | -0.24 [-0.45 - 1.61] | 0.32 | 0.79 [-0.45 - 1.72] | 0.06 | 0.18 [-0.6 - 3.61] | 0.177 |
| LDS | 0.04 [-0.06 - 0.95] | 2.80E-03 | 0.76 [-0.03 - 2.67] | 2.60E-05 | 2.35 [0.95 - 3.41] | 1.40E-08 | 3.57 [0.78 - 4.48] | 3.80E-08 |
| STL | 1.59 [0.33 - 3.4] | 2.80E-07 | 3.07 [1.37 - 4.76] | 1.00E-08 | 3.55 [1.88 - 6.89] | 2.40E-10 | 5.03 [2.2 - 7.34] | 2.20E-11 |
| CF | 1.15 [-0.29 - 2.3] | 1.30E-05 | 3.04 [1.64 - 5.8] | 1.30E-11 | 6.55 [4.58 - 8.8] | 6.60E-13 | 6.53 [5.58 - 8.8] | 5.90E-13 |
| NS | 2.39 [0.57 - 4.5] | 8.70E-18 | 3.07 [1.46 - 5.33] | 1.30E-23 | 3.69 [1.94 - 5.21] | 1.10E-25 | 5.78 [3.65 - 8.37] | 1.80E-28 |
| HPP | -0.27 [-0.39 - 0.6] | 0.054 | 0.54 [-0.34 - 1.03] | 2.60E-04 | 0.57 [-0.27 - 1.65] | 6.40E-06 | 1.36 [0.18 - 2.38] | 2.90E-07 |
| HHT | -0.05 [-0.21 - 0.74] | 8.90E-04 | 0.64 [0 - 2.77] | 1.60E-08 | 2.26 [1.58 - 3.88] | 8.60E-12 | 2.26 [1.49 - 4.77] | 7.80E-16 |
| ALL | 0.15 [-0.24 - 2.05] | 3.60E-31 | 1.45 [-0.01 - 3.64] | 9.10E-55 | 2.34 [0.66 - 4.65] | 3.80E-74 | 3.23 [1.22- 5.87] | 7.00E-84 |

| Disease | High score | | | |
|---|---|---|---|---|
| | Pre-suspicion | Pre-diagnosis* | Post-diagnosis | All |
| MFS (33) | 0 (0%) | 4 (12%) | 8 (24%) | 11 (33%) |
| cEDS (6) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| vEDS (13) | 1 (7.7%) | 2 (15%) | 0 (0%) | 2 (15%) |
| LDS (17) | 1 (5.9%) | 3 (18%) | 3 (18%) | 7 (41%) |
| STL (18) | 4 (22%) | 7 (39%) | 9 (50%) | 10 (56%) |
| CF (18) | 2 (11%) | 8 (39%) | 14 (78%) | 15 (83%) |
| NS (49) | 13 (27%) | 19 (39%) | 20 (41%) | 32 (65%) |
| HPP (30) | 0 (0%) | 1 (3.3%) | 2 (6.7%) | 3 (10%) |
| HHT (32) | 1 (3.1%) | 5 (16%) | 6 (19%) | 10 (31%) |
| ALL (216) | 22 (10%) | 48 (22%) | 62 (29%) | 90 (42%) |

* includes pre-suss and pre-dx


cEDS
CF
HHT
HPP
LDS
MFS
NS
STL
vEDS
rPheRS
10
5
0
Pre-suspicion
Pre-diagnosis
Post-diagnosis
All


A
age at diagnosis (years)
0
20
40
60
80
CF
HPP
vEDS
HHT
LDS
MFS
cEDS
STL
NS


MFS
LDS
vEDS
CF
HHT
cEDS
HPP
STL
NS
16%
33%
51%
27%
26%
47%
28%
22%
50%
29%
25%
45%
29%
27%
44%
33%
17%
50%
38%
15%
47%
39%
16%
45%
44%
14%
41%
0%
25%
50%
75%
100%
phenotypes first ascertained during time interval
Time interval
Pre-suspicion
Suspicion to diagnosis
Post-diagnosis

# Time interval

- The median time from first visit to clinical suspicion was 3.23 years (IQR: 153 days-6.4 years)
- The median time from clinical suspicion to diagnosis was 71 days (IQR: 20.8-235)

# Physician‘s view

- We not usually enter ICD10 of all symptoms
- How about SNOMED CT?
- When we would change from scanning medical records to EMR?
- Cluster/Family analysis

# THANK YOU