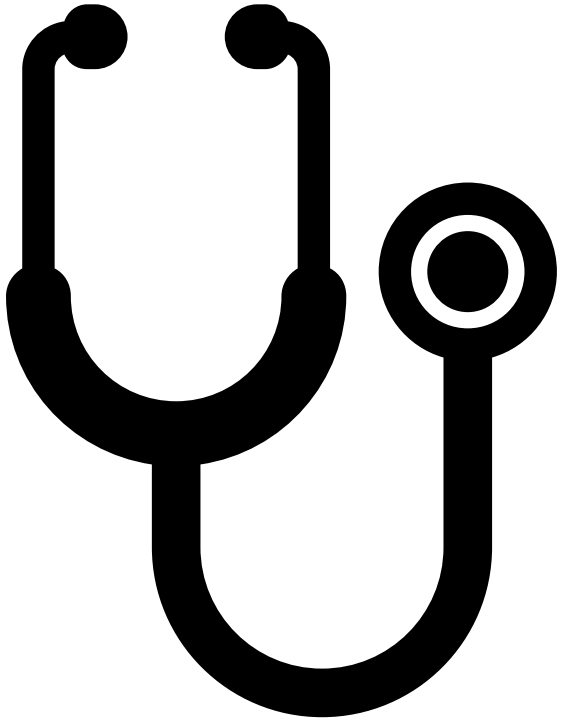
# Medicina personalizzata nelle arteriopatie/aortopatie ereditarie: il percorso diagnostico-terapeutico-assistenziale

*Martina Berteotti, MD, PhD*

*Università degli studi di Firenze*

# Percorso diagnostico



# Thoracic aortic aneurysms

- TAAs occur in 5 to 10 per 100 000 person years
- Aortic aneurysms and dissections are estimated to account for 1–2% of all deaths in Western countries. The true incidence might even be higher.

| |
|---|
| HTAD (see Table 7): syndromic<br>Marfan syndrome<br>Loeys-Dietz syndrome<br>Vascular Ehlers-Danlos syndrome<br>Smooth muscle dysfunction syndrome<br>Others: attributable to pathogenic variants in FLNA, BGN, LOX |
| HTAD (see Table 7): nonsyndromic<br>ACTA2, MYH11, PRKG1, MYLK, and others<br>Familial thoracic aortic aneurysm without identified pathogenic variants in a known gene for HTAD |
| Congenital conditions<br>Bicuspid aortic valve<br>Turner syndrome<br>Coarctation of the aorta<br>Complex congenital heart defects (tetralogy of Fallot, transposition of the great vessels, truncus arteriosus) |
| Hypertension |
| Atherosclerosis |
| Degenerative |
| Previous aortic dissection |
| Inflammatory aortitis<br>Giant cell arteritis<br>Takayasu arteritis<br>Behçet disease<br>Immunoglobulin G4-related disease, antineutrophil cytoplasmic antibody-related, sarcoidosis |
| Infectious aortitis<br>Bacterial, fungal, syphilitic |
| Previous traumatic aortic injury |

# Heritable thoracic aortic diseases

- Approximately 20% of TAA are related to a genetic or heritable condition
    - Associated with multisystem features (**syndromic HTAD**)
    - Abnormalities limited to aorta with or without its branches (**nonsyndromic HTAD**)

**Table 1**. Syndromic and Nonsyndromic Aneurysm Conditions (Table view)

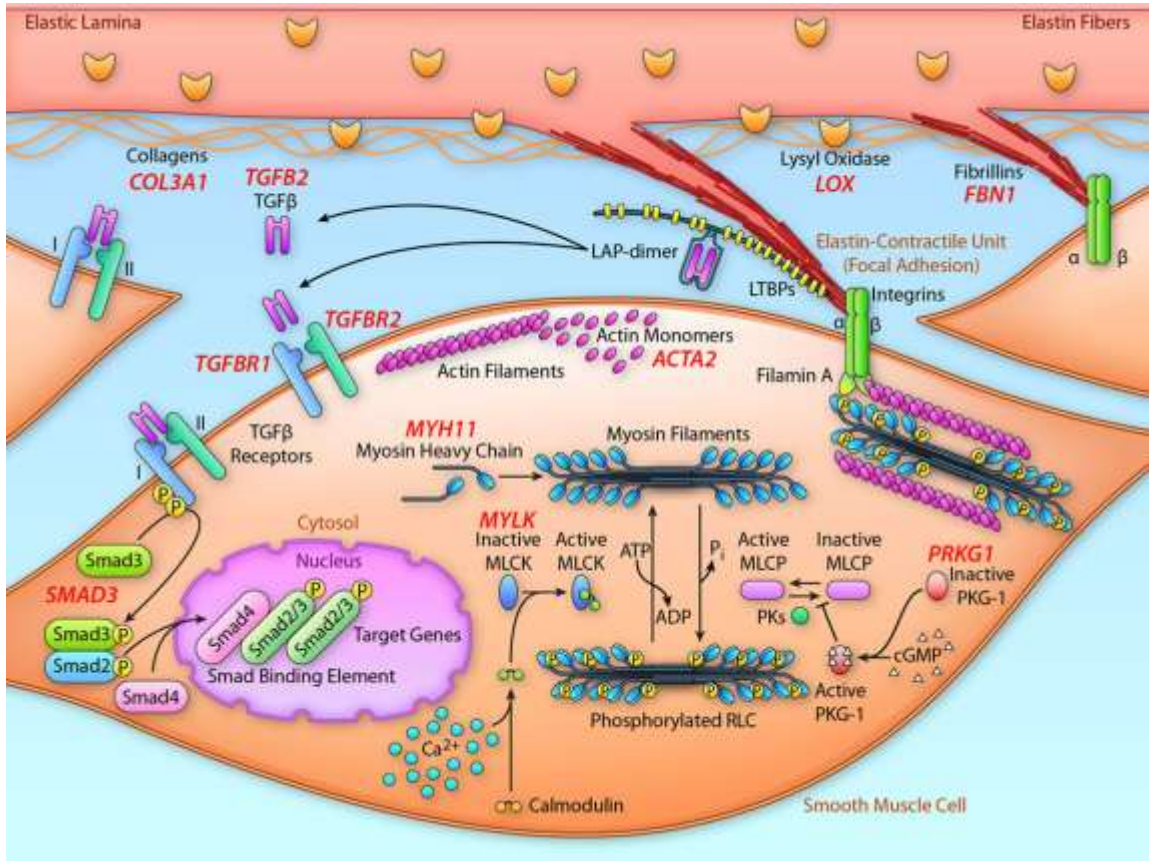
EPUB

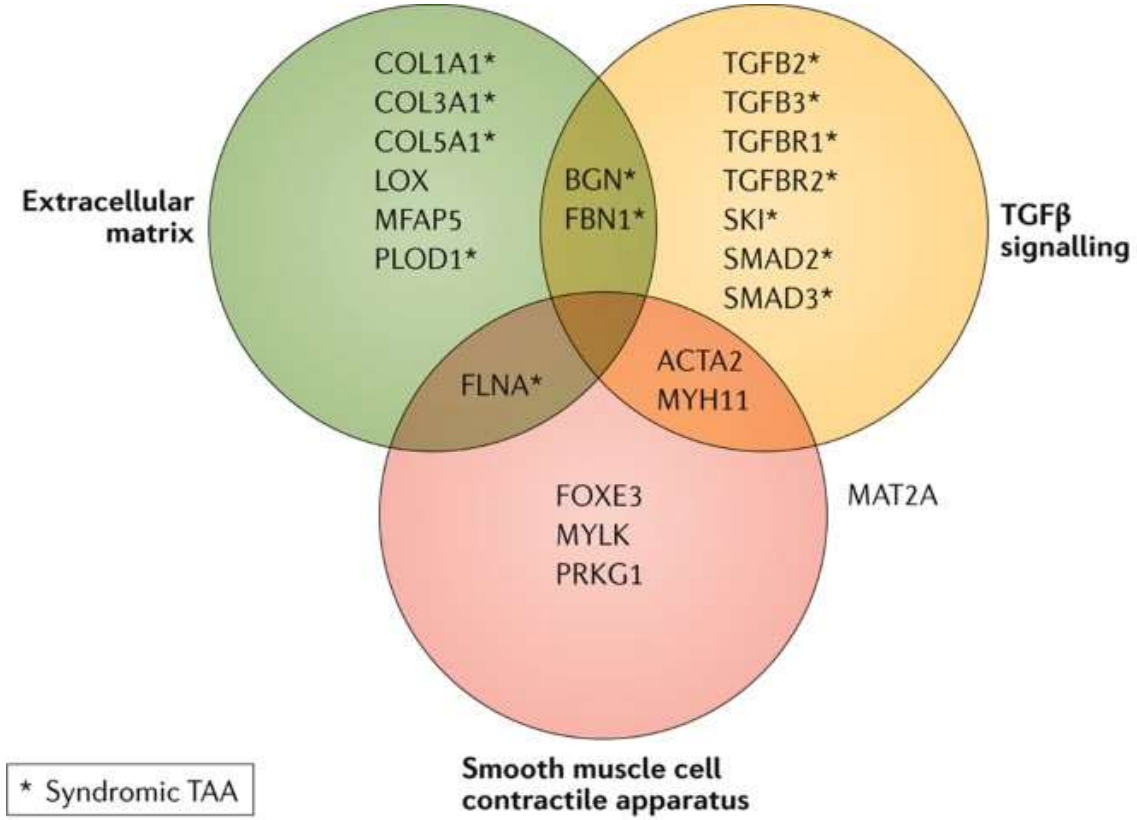
| Syndromic Aneurysm Conditions | Nonsyndromic Aneurysm Conditions |
|---|---|
| MFS | FTAAD |
| LDS | |
| Vascular Ehlers-Danlos syndrome, | Familial TAA |
| Shprintzen-Goldberg syndrome | |
| Aneurysms-osteoarthritis syndrome | BAV with aneurysm |
| Cutis laxa with aneurysm | |

Circulation. 2016;133:2516-2528.

# Genetic

These genes explain <30% of all cases of familial TAA




Nature Reviews Cardiology volume 14, pages 197–208 (2017)

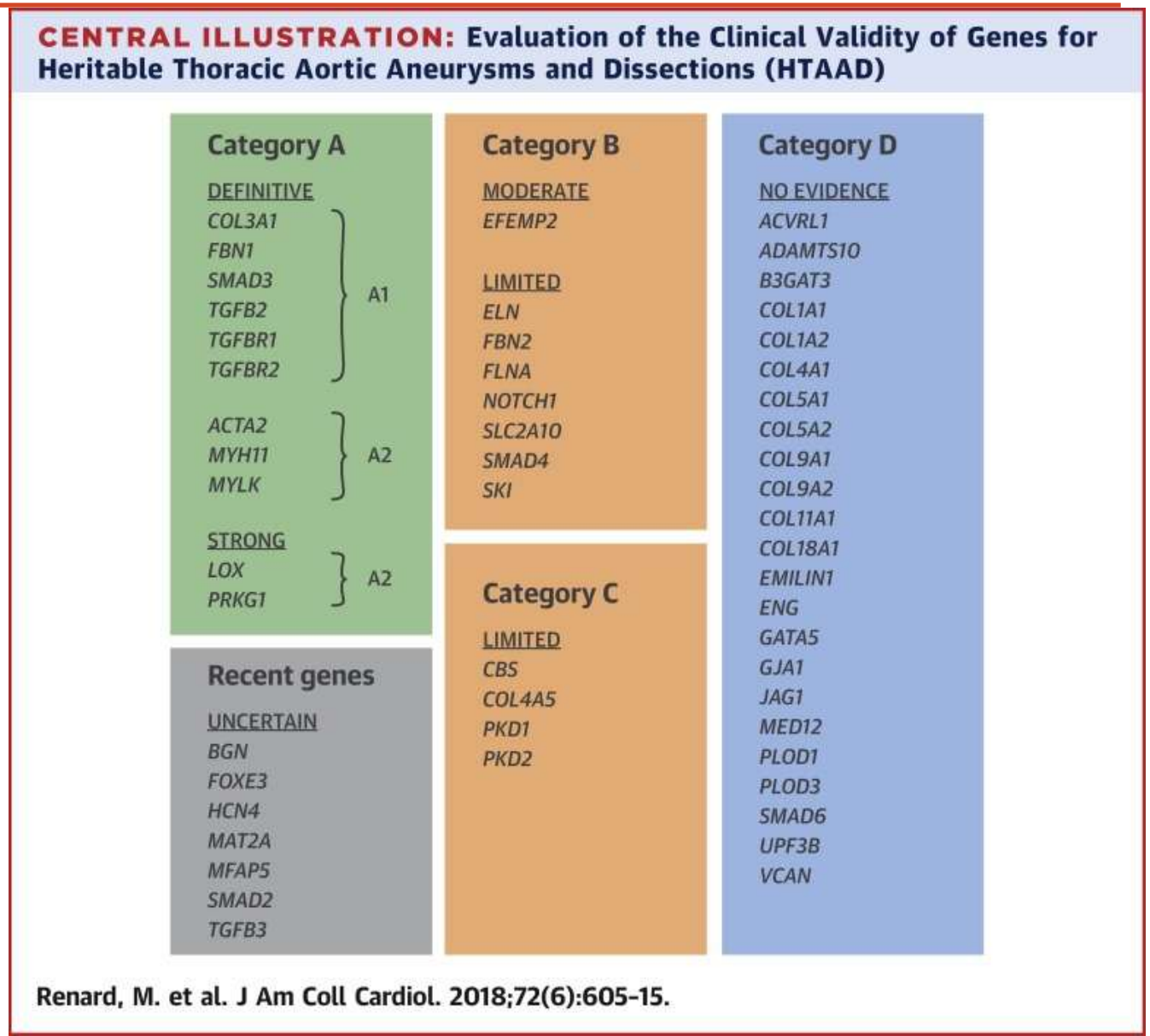
# HTADs genes

**Categories A1 and A2**: "HTAAD genes"

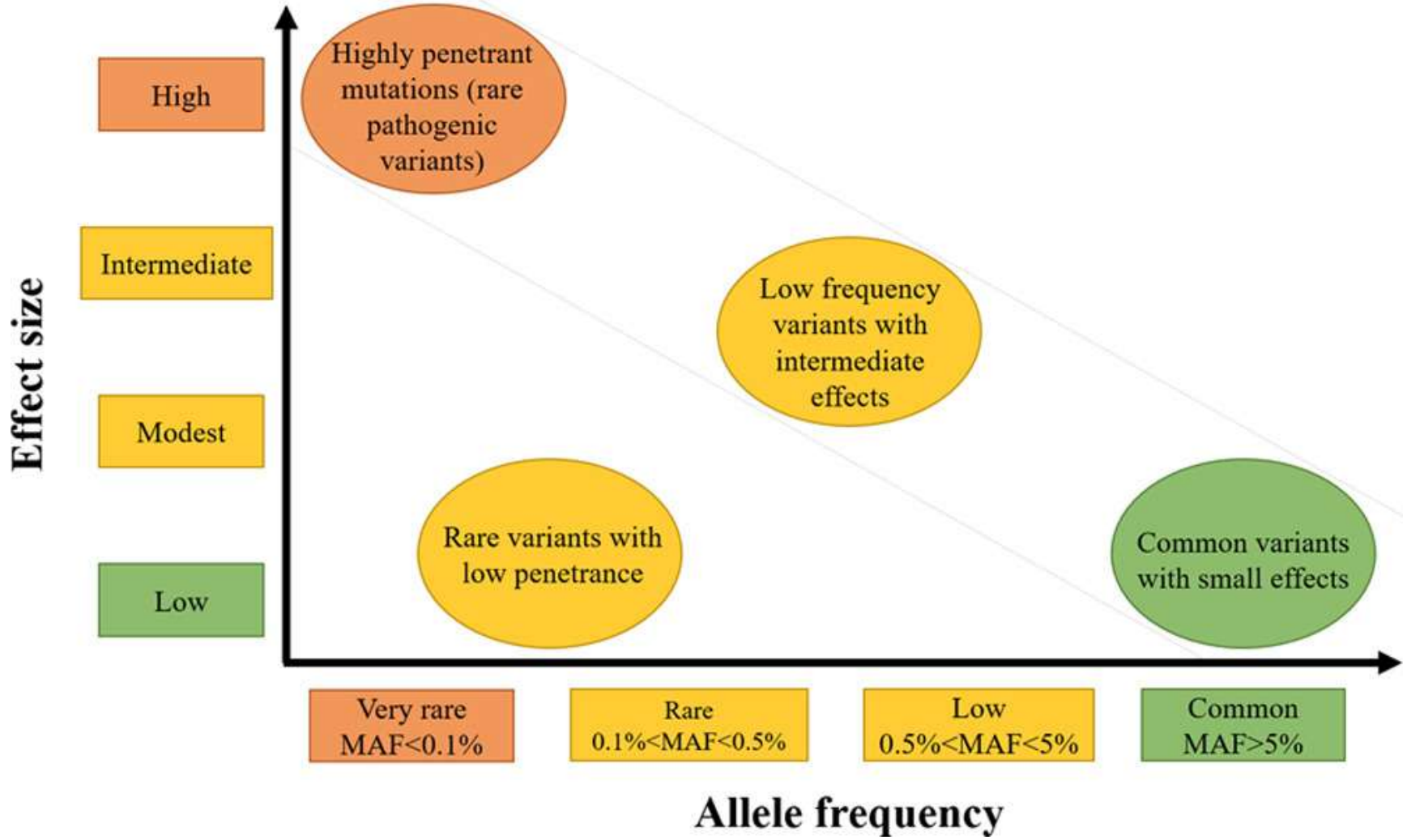
**Category B**: "Potentially diagnostic genes," which may allow diagnosis of the cause of thoracic aortic enlargement, but primarily associated with other clinical features and which do not carry significant risks of progression to aortic dissection

**Category C**: genes with limited evidence as a Mendelian cause of HTAAD where diagnosis is primarily based on nonvascular features

**Category D**: genes for which some experimental data may suggest a link with thoracic aortic disease but no clinical evidence is available.



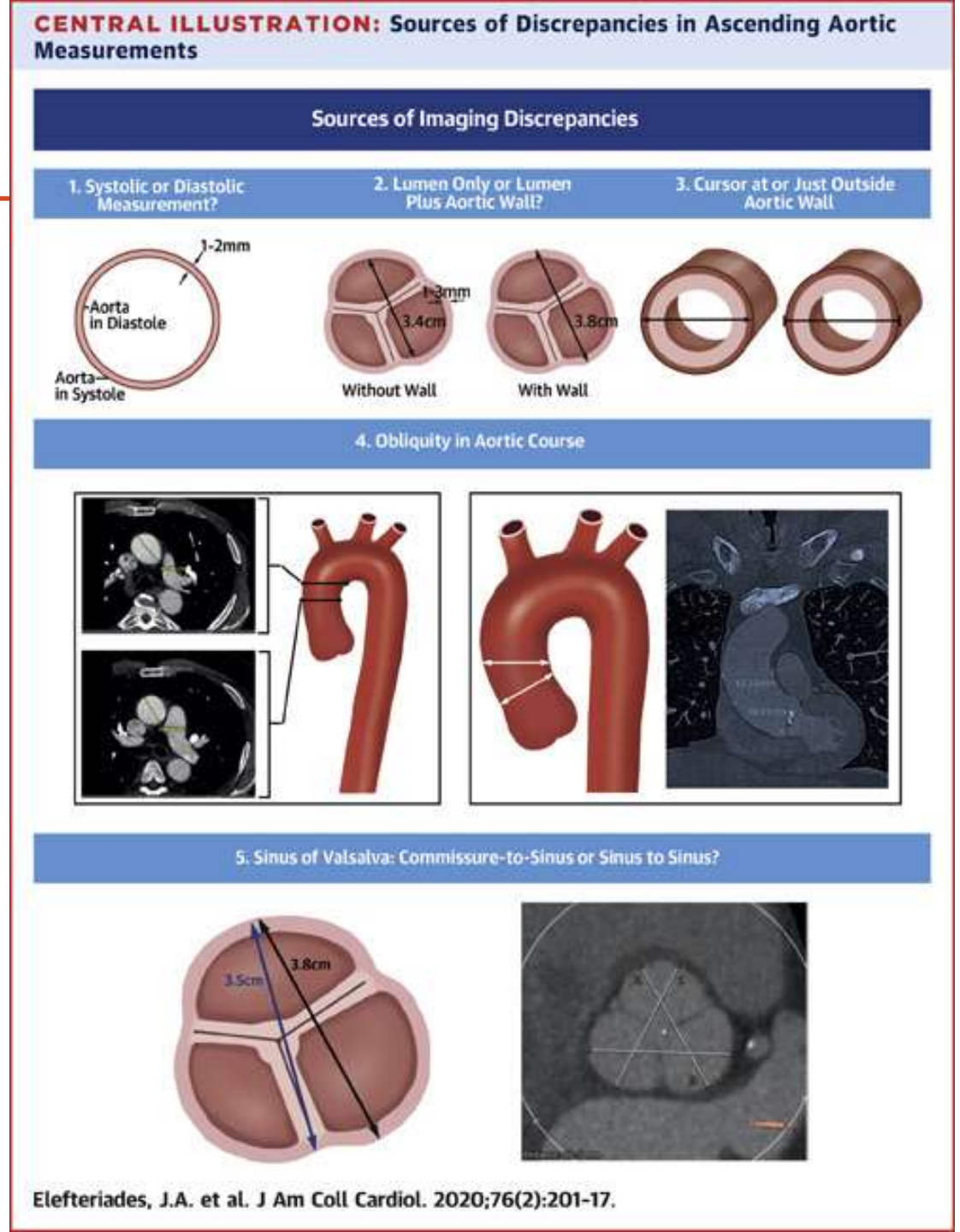
# Thoracic aortic disease risk associated to variant frequencies




Circulation Research. 2019;124:588–606

# Indication for aortic measurement

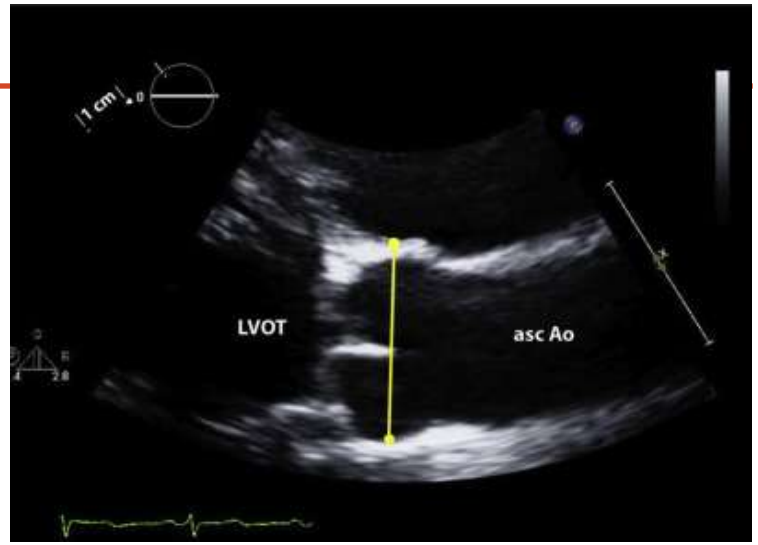
- Echocardiography
- Angio-TC
- Angio- RM



# Indication for aortic measurement

HTAD patient pathway: Strategy for diagnostic work-up of patients and families with (suspected) heritable thoracic aortic diseases (HTAD). A statement from the HTAD working group of VASCERN

Maryanne Caruana [a], Marieke J. Baars [b], Evy Bashiardes [c], Kalman Benke [d], Erik Björck [e], Andrei Codreanu [f], Elena de Moya Rubio [g], Julia Dumfarth [h], Arturo Evangelista [i], Maarten Groenink [b], Klaus Kallenbach [f], Marlies Kempers [j], Anna Keravnou [c], Bart Loeys [k], Laura Muiño-Mosquera [l], Edit Nagy [m], Olivier Milleron [n], Stefano Nistri [o], Guglielmina Pepe [o], Jolien Roos-Hesselink [p], Zoltan Szabolcs [d], Gisela Teixidó-Tura [i], Janneke Timmermans [j], Ingrid Van de Laar [p], Roland van Kimmenade [j], Aline Verstraeten [k], Yskert Von Kodolitsch [q], Julie De Backer [l], Guillaume Jondeau [n,*]




- **Leading edge to leading edge** measurements in diastole are preferred
- When comparing serial studies to analyse for progression of aortic dilatation over time, side-by-side comparison of measurements using the same imaging modality and assessment method is recommended. Only differences in **excess of 3 mm** are to be considered significant.
- **Z score** (>2 adult, >3 <18 yo)
    - Campens et al 2014
    - Devereux et al, 2012 for severely under/overweight

# Genetic testing

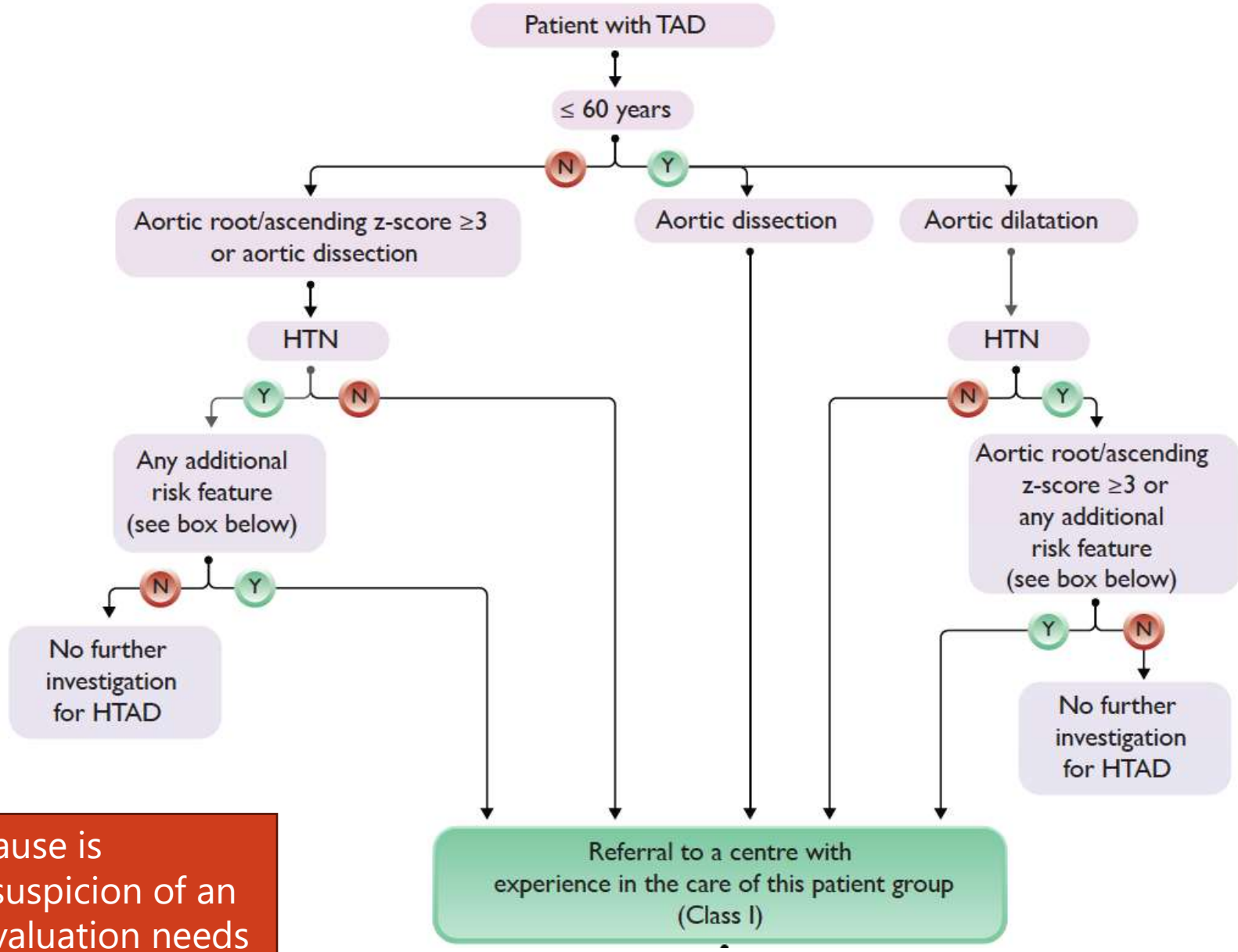
**Any additional risk feature**

**Syndromic features of:**

- Marfan syndrome
- Loeys-Dietz syndrome
- Vascular Ehlers-Danlos syndrome

**Family history of (either one):**

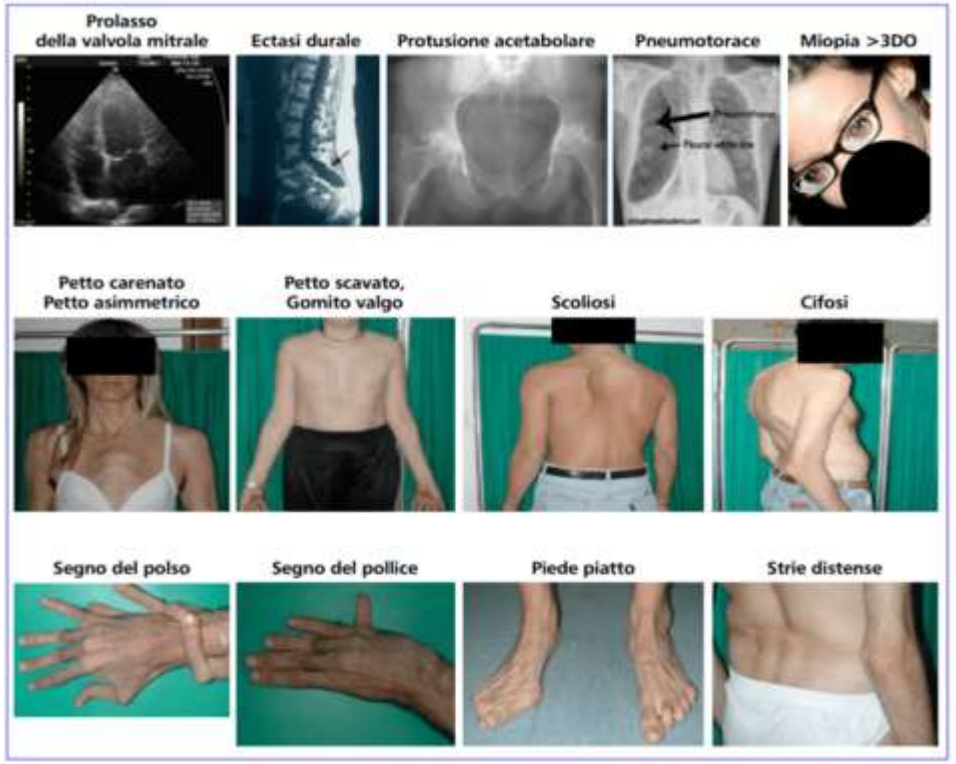
- TAD
- Peripheral/intracranial artery aneurysm
- Unexplained Sudden death <60 years




In those patients in whom no genetic cause is identified, but in whom there is a high suspicion of an underlying genetic defect, genetic re-evaluation needs to be considered after 3–5 years.

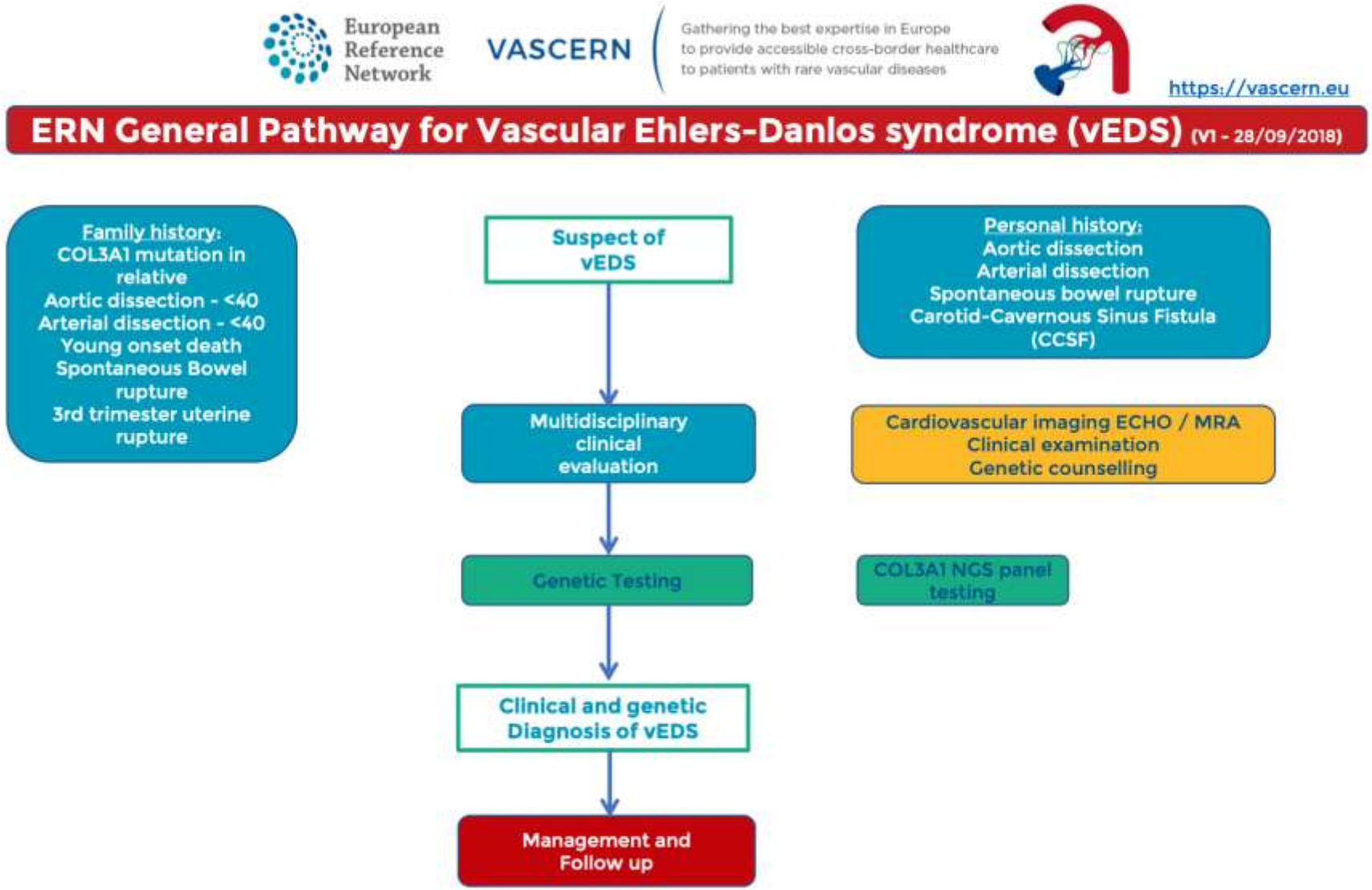
# Referred to an expert centre for further evaluation of possible HTAD

| | |
|---|---|
| **A first-degree family member with a HTAD +/- pathogenic variant in a gene known to cause HTAD** | at least one first or second-degree relative with a thoracic aortic aneurysm or dissection <70 years or sudden death <45 years in the absence of an alternative etiology |
| **Ectopia lentis without other obvious explanation** | |
| **A systemic score >5 in adults and >3 in children** | intracerebral arterial aneurysms, simple renal cysts at an early age, congenital mydriasis, or congenital heart defects such as BAV, coarctation of the aorta and persistent ductus arteriosus should also raise suspicion. |
| **A combination of features typical of LDS** | bifid uvula, craniosynostosis, hypertelorism or osteoarthritis |




European Journal of Medical Genetics 66 (2023) 104673

# V-EDS


European Reference Network
VASCERN
Gathering the best expertise in Europe to provide accessible cross-border healthcare to patients with rare vascular diseases
https://vascern.eu
ERN General Pathway for Vascular Ehlers-Danlos syndrome (vEDS) (V1 - 28/09/2018)
Family history:
COL3A1 mutation in relative
Aortic dissection - <40
Arterial dissection - <40
Young onset death
Spontaneous Bowel rupture
3rd trimester uterine rupture
Suspect of vEDS
Personal history:
Aortic dissection
Arterial dissection
Spontaneous bowel rupture
Carotid-Cavernous Sinus Fistula (CCSF)
Multidisciplinary clinical evaluation
Cardiovascular imaging ECHO / MRA
Clinical examination
Genetic counselling
Genetic Testing
COL3A1 NGS panel testing
Clinical and genetic Diagnosis of vEDS
Management and Follow up

# Diagnosis

## The 2010 Revised Ghent Nosology for Marfan syndrome relies on seven rules as indicated below:

IN THE ABSENCE OF FAMILY HISTORY:

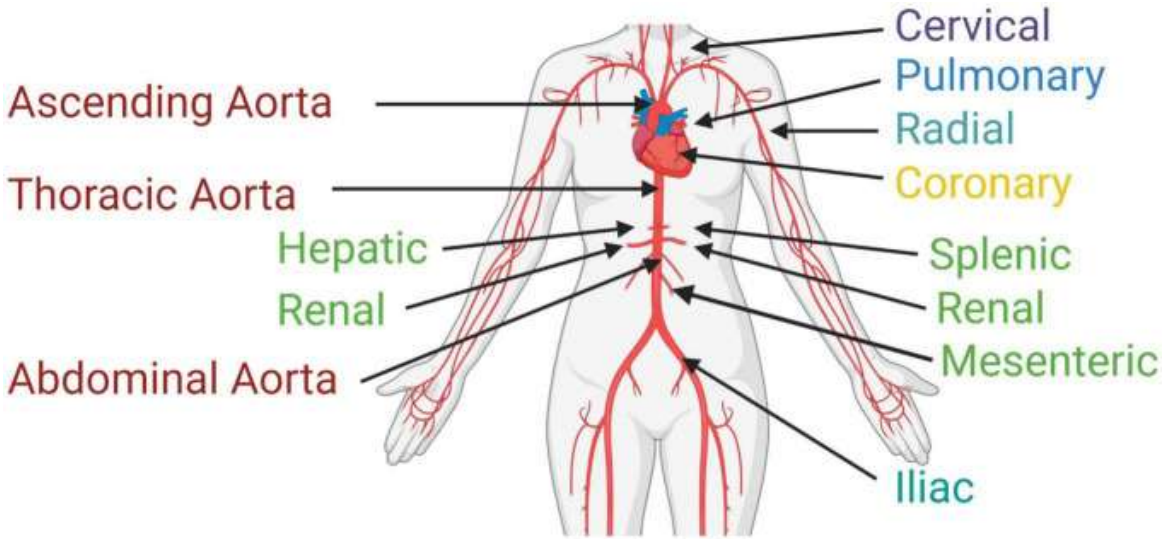
1. **Aortic Root Dilatation Z score ≥ 2 AND Ectopia Lentis = Marfan syndrome –** The presence of aortic root dilatation (Z-score ≥ 2 when standardized to age and body size) or dissection and ectopia lentis allows the unequivocal diagnosis of Marfan syndrome, regardless of the presence or absence of systemic features except where these are indicative of Shprintzen Goldberg syndrome, Loeys-Dietz syndrome, or vascular Ehlers Danlos syndrome.

2. **Aortic Root Dilatation Z score ≥ 2 AND FBN1 = Marfan syndrome –** The presence of aortic root dilatation (Z ≥ 2) or dissection and the identification of a bona fide FBN1 mutation are sufficient to establish the diagnosis, even when ectopia lentis is absent.

3. **Aortic Root Dilatation Z score ≥ 2 AND Systemic Score ≥ 7pts = Marfan syndrome –** Where aortic root dilatation (Z ≥ 2) or dissection is present, but ectopia lentis is absent and the FBN1 status is either unknown or negative, a Marfan syndrome diagnosis is confirmed by the presence of sufficient systemic findings (≥ 7 points, according to a scoring system) confirms the diagnosis. However, features suggestive of Shprintzen Goldberg syndrome, Loeys-Dietz syndrome, or vascular Ehlers Danlos syndrome must be excluded and appropriate alternative genetic testing (TGFBR1/2, SMAD3, TGFB2, TGFB3, collagen biochemistry, COL3A1, and other relevant genetic testing when indicated and available upon the discovery of other genes) should be performed.

4. **Ectopia lentis AND a FBN1 mutation associated with Aortic Root Dilatation = Marfan syndrome –** In the presence of ectopia lentis, but absence of aortic root dilatation/dissection, the identification of an FBN1 mutation previously associated with aortic disease is required before making the diagnosis of Marfan syndrome.

# Arterial dissections are reported in large- and medium-sized arteries




| Artery | Intimal Medial Thickness (mm) | Reported Incidence Rates | References |
|---|---|---|---|
| **Ascending Aorta** | 1.48 | Most Common<br>10 cases/100,000 person-years (thoracic); Ascending more common than descending | Bae 2003<br>Saliba 2015<br>Roberts 1991 |
| **Descending Aorta** | 1.39 | | |
| **Abdominal Aorta** | 1.24 | Least Common Aortic Dissection Subtype | Sumbul 2019<br>Roberts 1991 |
| **Coronary Artery** | 0.75 | Less Common<br>2.7 cases/100,000 person-years | Fayad 2000<br>Kronzer 2020 |
| **Cervical Artery** | 0.66 | Less Common<br>2.6 cases/100,000 person-years | Eigenbrodt 2007<br>Lee 2006 |
| **Renal Artery** | 0.50 | Rare<br>Estimated 1-2% arterial dissections | Leertouwer 1999<br>Jha 2020 |
| **Pulmonary Artery** | 0.16 | Very Rare<br>~150 cases reported | Li 2012<br>Fernando 2019 |

Front Cardiovasc Med. 2022 Dec 6;9:1055862.

# Arterial dissection associated conditions

| Condition | Description | Genes with pathogenic variants | Prevalence | Sexual dimorphism | | |
|---|---|---|---|---|---|---|
| Ehlers–Danlos (EDS) | CTD; hyperextendable joints, hyperextensible skin, easy bruising, abnormal scarring; vascular EDS subtype, and in 17% 13 non-vascular EDS have vascular involvement | *COL1A1, COL1A2, COL5A1, COL5A2, COL3A1, COL12A, ADAMTS2, PLOD1, FKBP14, TNXB, CHST14, DSE, B4GALT7, B3GALT6, SLC39A13, ZNF469, PRDM5, C1R, C1S, AEBP1* | 1:5,000 | Dissection type vary by gender | | |
| Marfan syndrome | CTD; affects the ocular, skeletal, and cardiovascular systems with varying severity | *FBN1* | 1:5,000–1:10,000 | Sex related burden (pregnancy increases aortic root dilation) | SCAD, PA | 269–272) |
| Loeys-Dietz syndrome | CTD; affects the skin, skeletal and cardiovascular system | *TGFBR1, TGFBR2, SMAD3, TGFB2* | Less than 1:10,000 | NA | CeAD, aortic, SCAD | (273–275) |
| Alport syndrome | Affects the renal, auditory and ocular systems. Hypertension increases risk of cardiovascular events 1000 fold. | *COL4A3, COL4A4, COL4A5* | 1:10,000 | X-linked in 85% cases | Aortic, SCAD | (276–279) |
| Fibromuscular dysplasia | Abnormal (dysplastic) cell growth in medium-sized arteries causing tortuosity | *PHACTR1* | Up to 6.6% population (potential kidney donors) | 90% patients female; male patients significantly associated with CeAD | CeAD, SCAD | (157, 166, 171, 280, 281) |
| Polycystic kidney disease | Kidney cyst formation, cardiovascular | *PKD1, PKD2* | 10M people globally | NA | CeAD, Aortic, SCAD, iliac | (34, 175, 282–284) |
| Osteogenesis imperfecta | Brittle bones disease | *COL1A1, COL1A2, BMP1, CRTAP, LEPRE1, PPIB, TMEM38B, SERPINH1, FKBP10, PLOD2, WNT1, CREB3L1* | 1:20,000 | NA | CeAD, aortic, SCAD | (229, 285–289) |

## Survival is affected by mutation type and molecular mechanism in vascular Ehlers–Danlos syndrome (EDS type IV)

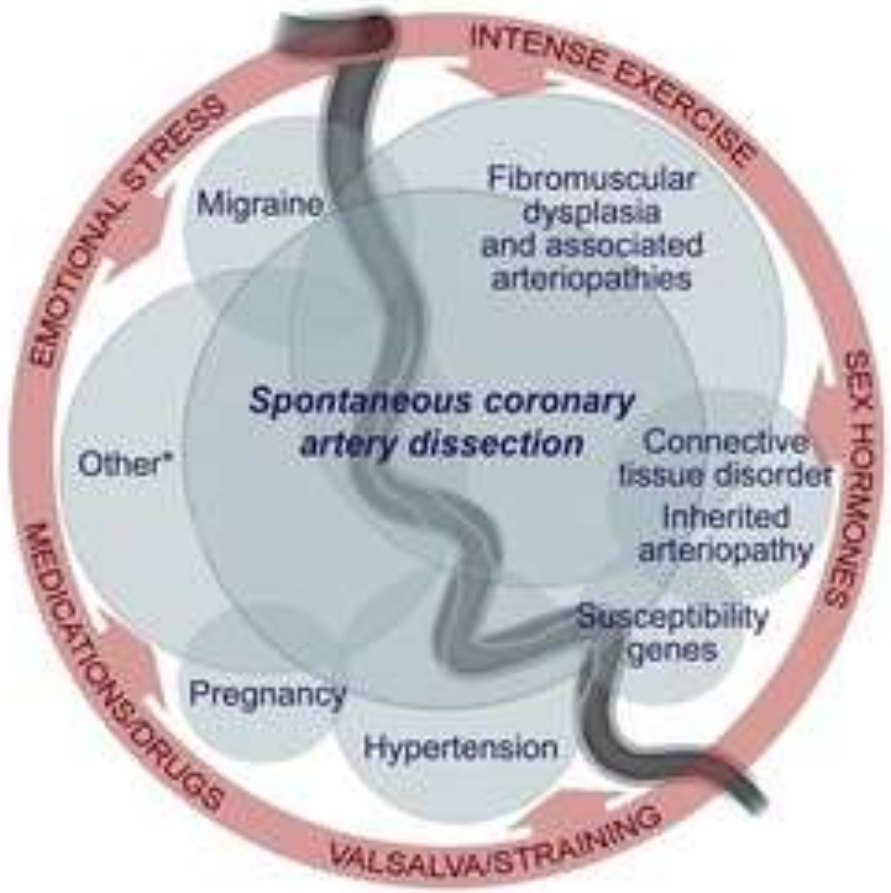
Melanie G. Pepin, MS[1], Ulrike Schwarze, MD[1], Kenneth M. Rice, PhD[2], Mingdong Liu, PhD[2], Dru Leistritz, MS[1] and Peter H. Byers, MD[1,3]

572 pts
Aortic dissection: 75% men
SCAD and CeAD: 61% and 81% women

*Genet Med.*(2014) 16:881–8.

# Spontaneous coronary dissection

- 4% of patients presenting with ACS, up to 35% of all ACS cases in women ≤50 years of age.




| Associated Condition or Factor | Reported Prevalence in Cohort Studies, % |
|---|---|
| Fibromuscular dysplasia | 25–86[13,29,33,34] |
| Pregnancy | 2–8[8,9,13,33] |
| Multiparity (≥4 births) | 8.9–10[13,33] |
| Inherited arteriopathy and connective tissue disorder (see Table 4) | 1.2–3.0[8,13] |
| Marfan syndrome, Loeys-Dietz syndrome, vascular Ehlers-Danlos syndrome, $\alpha_1$-antitrypsin deficiency, polycystic kidney disease | |
| Exogenous hormones | 10.7–12.6[8,13] |
| Oral contraceptives, postmenopausal therapy, infertility treatments, testosterone, corticosteroids | |
| Systemic inflammatory disease | <1–8.9[9,13] |
| Systemic lupus erythematosus, Crohn disease, ulcerative colitis, polyarteritis nodosa, sarcoidosis, Churg-Strauss syndrome, Wegener granulomatosis, rheumatoid arthritis, Kawasaki disease, celiac disease | |
| Migraine headache | NR |
| Coronary artery spasm | NR |
| Precipitating factors | >50% Patients recall a precipitating factor[13] |
| Intense exercise (isometric or aerobic) | |
| Intense Valsalva | |
| Retching, vomiting, bowel movement, coughing, lifting heavy objects | |
| Intense emotional stress | |
| Labor and delivery | |
| Recreational drugs (cocaine, methamphetamines) | |
| Exogenous hormones/hormone modulators | |
| β-hCG injections, corticosteroid injections, clomiphene | |

Hayes, S.N. et al. J Am Coll Cardiol. 2020;76(8):961-84.

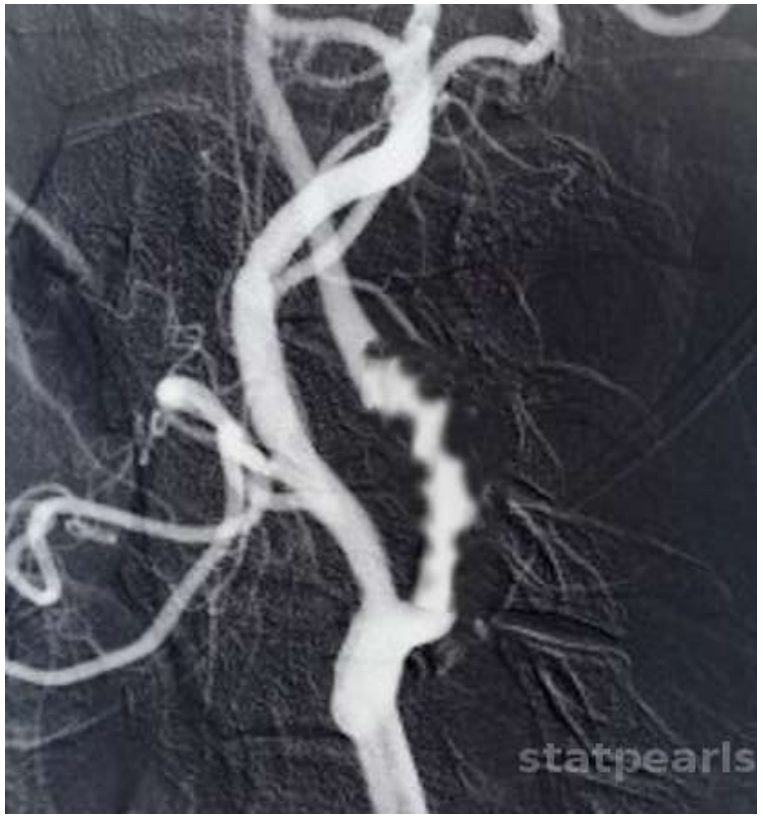
# Fibromuscolar displasya

FMD is an **idiopathic, non-inflammatory, non-atherosclerotic disease** affecting the musculature of the small- and medium-sized arterial walls and causing stenosis, aneurysms or dissections of the vascular territories.

**Pravalence**: renal FMD 0.4 %, craniocervical FMD 0.1%.

Can affect any artery:

- renal arteries 58%
- craniocervical arteries 32%
- other arterial beds 10%

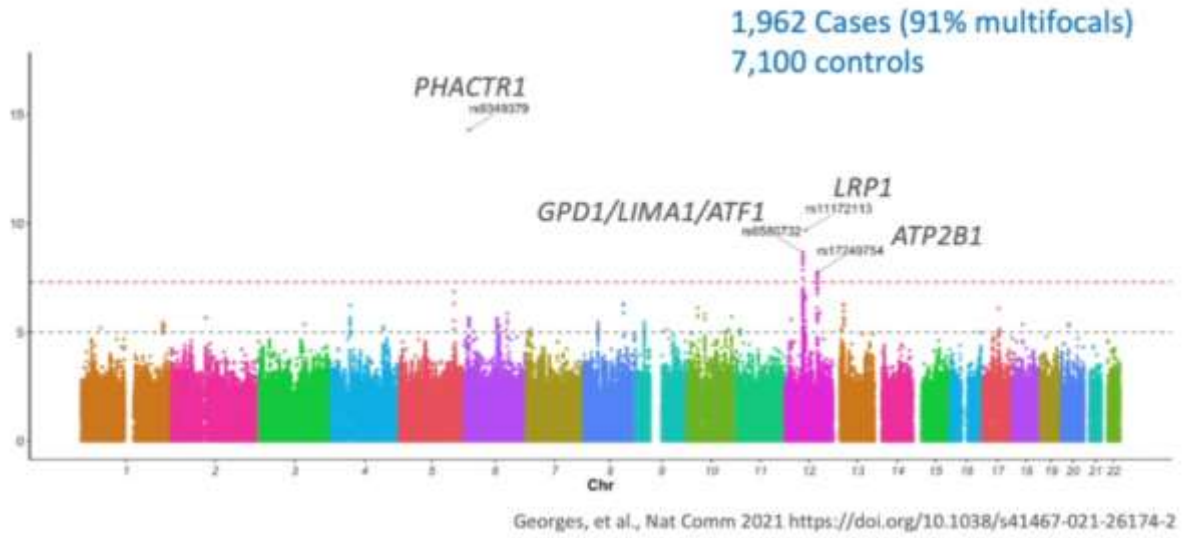


# Genetic

FMD appears to be both sporadic and familial in a subset of patients, with AD inheritance suggested in some families.

1.9–7.3% of patients with FMD report an affected family member.

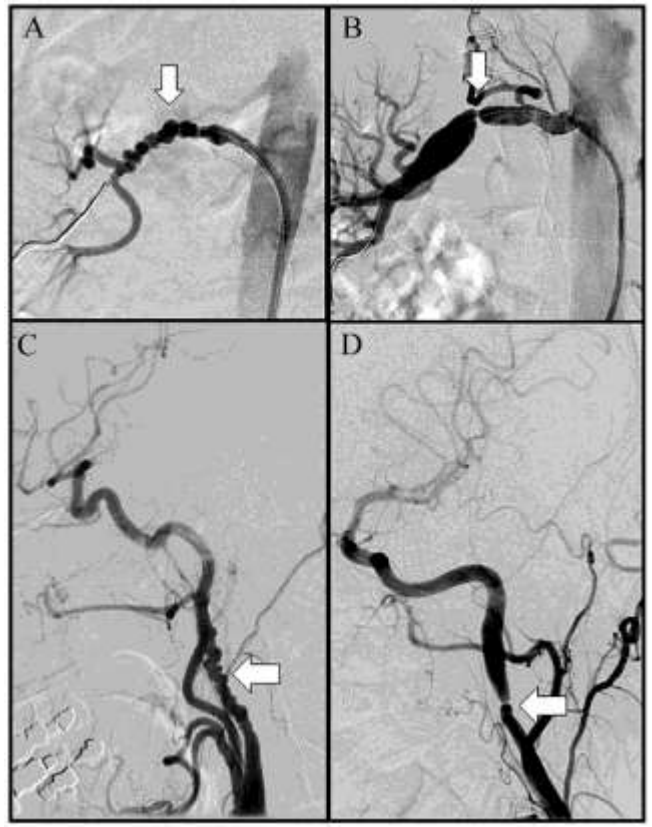
There are **currently no genetic tests** that are specific to FMD, and there is no justification for genetic testing of asymptomatic relatives of patients with FMD at this time.




Georges, et al., Nat Comm 2021 https://doi.org/10.1038/s41467-021-26174-2

# SCAD e FMD

- 29–70% of SCAD patients with FMD extracoronary lesions had involvement of two or more vascular beds.
- Extracoronary FMD associated with SCAD mostly, if not only, of the multifocal type.

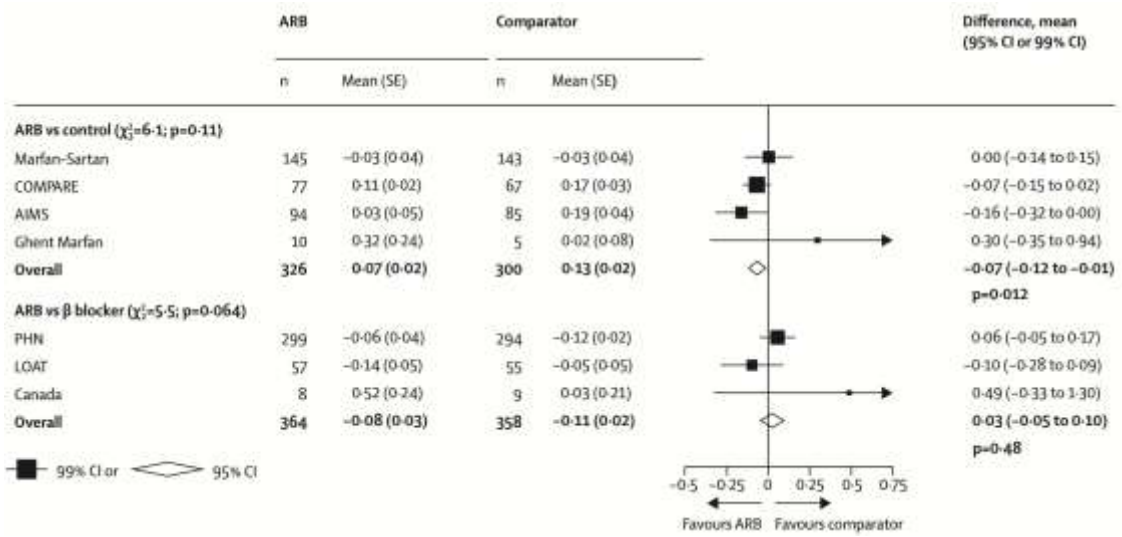



**Patients who have had SCAD should undergo imaging of all vessels from brain to pelvis, at least once and usually with CTA or contrast-enhanced MRA, to assess for FMD and other non-coronary arterial abnormalities.**

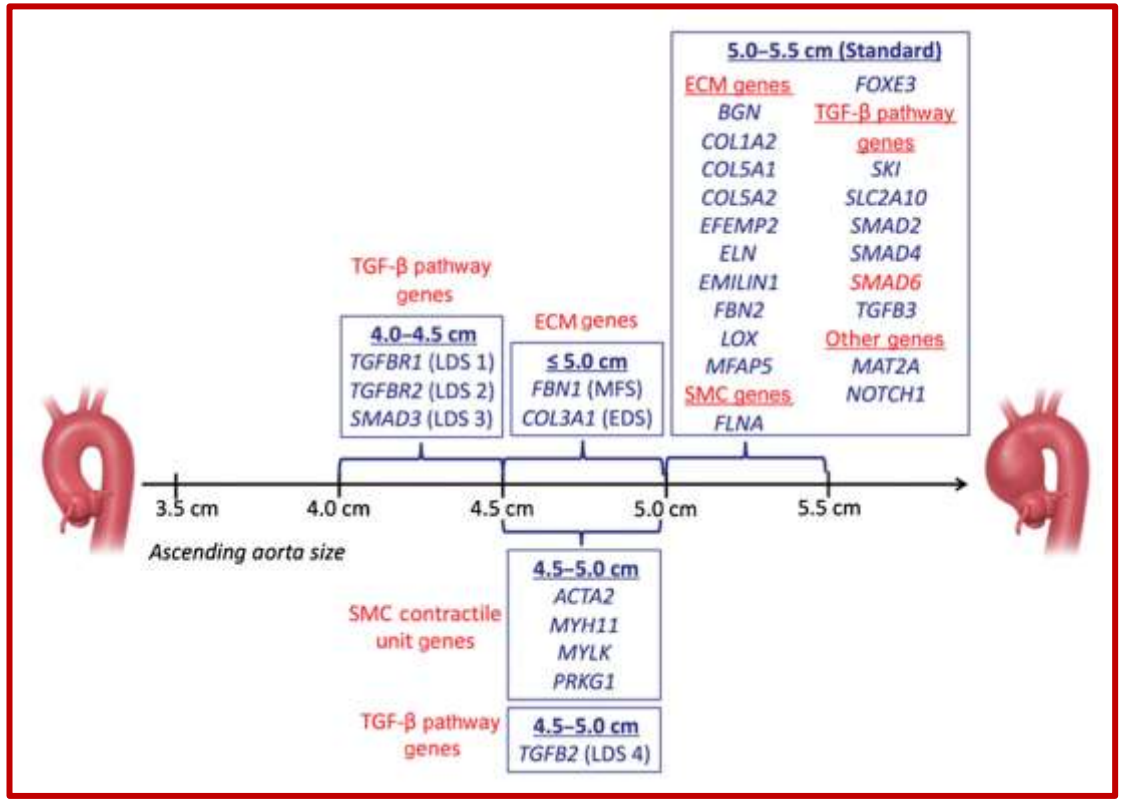
# Percorso terapeutico

# Terapia

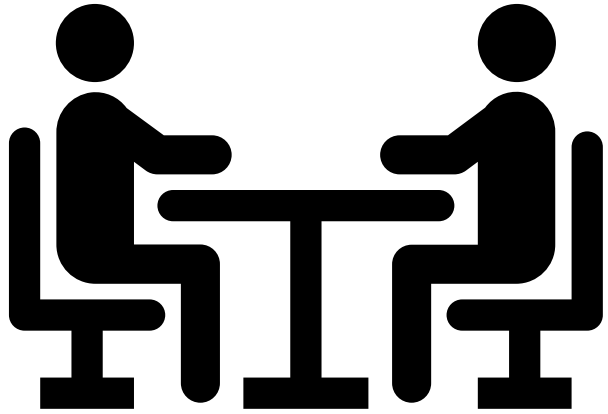
## Medical therapy



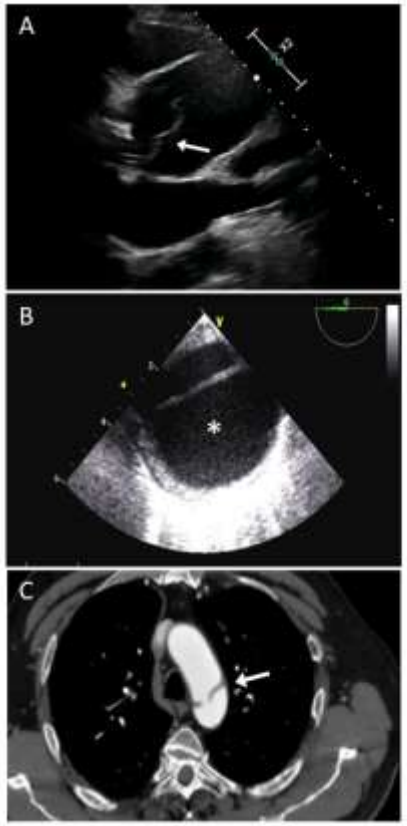

## Cardiac surgery

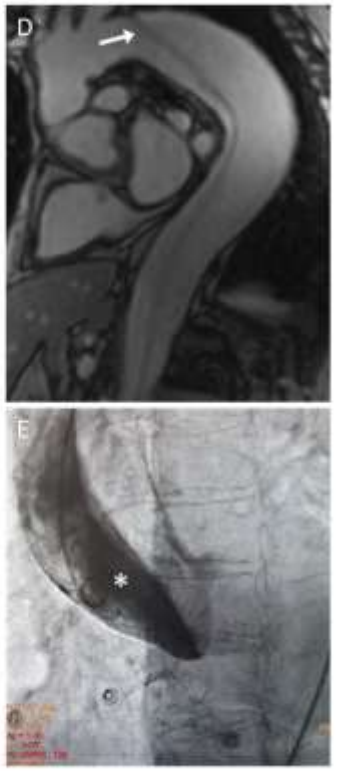


# Percorso assistenziale



# Timing imaging



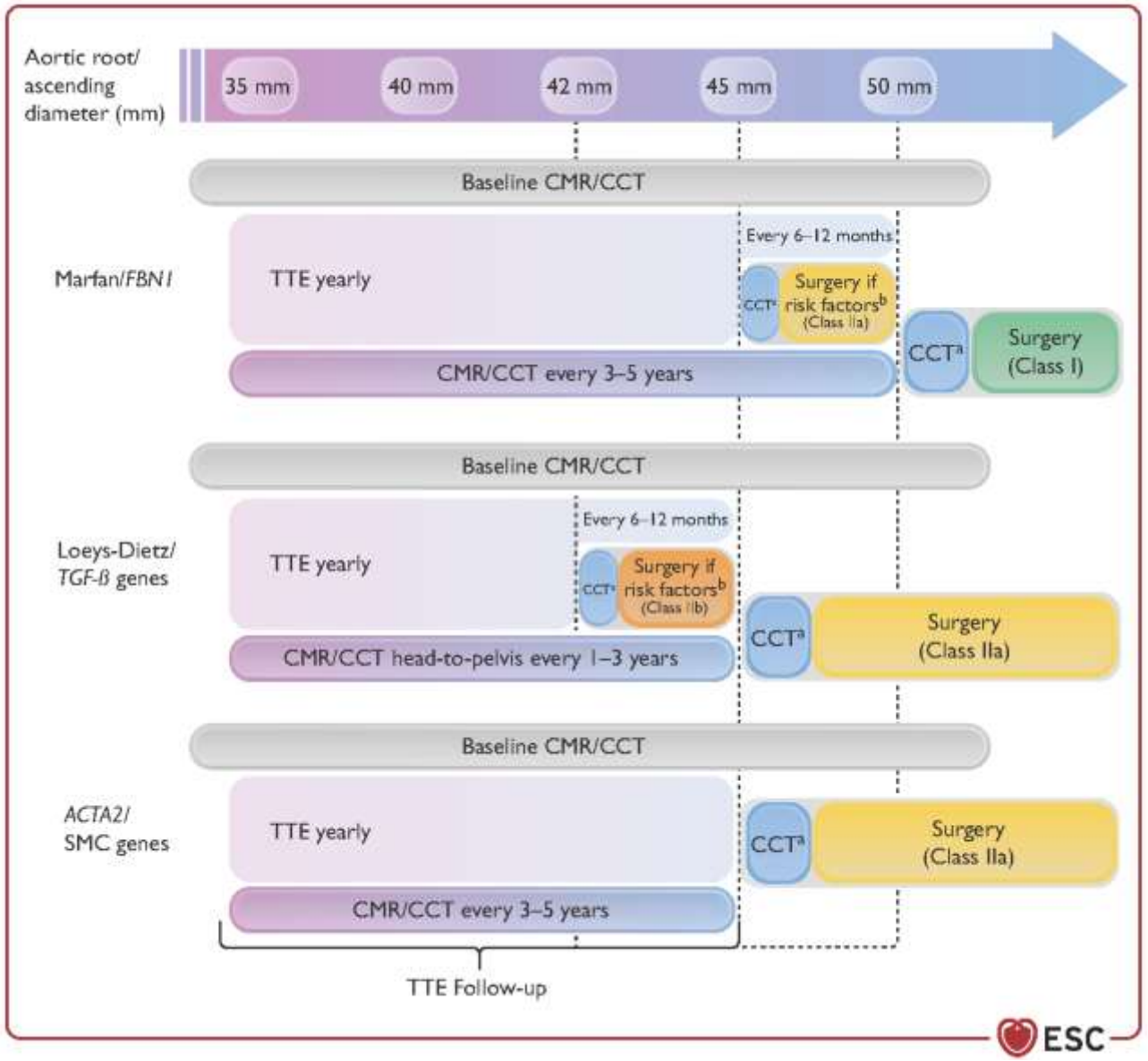



# Figure 41

## Algorithm for imaging surveillance in patients with syndromic and non-syndromic heritable thoracic aortic disease

**Risk factors:**

- aortic root diameter 40-45 mm and family history of aortic dissection <50 mm;
- resistant hypertension
- rapid growth of the aorta (annualized rate ≥3 mm in adults).




2024 ESC Guidelines for the management peripheral arterial and aortic diseases
(European Heart Journal; 2024 – doi: 10.1093/eurheartj/ehae179)

# Gestione comorbidità in forme sindromiche

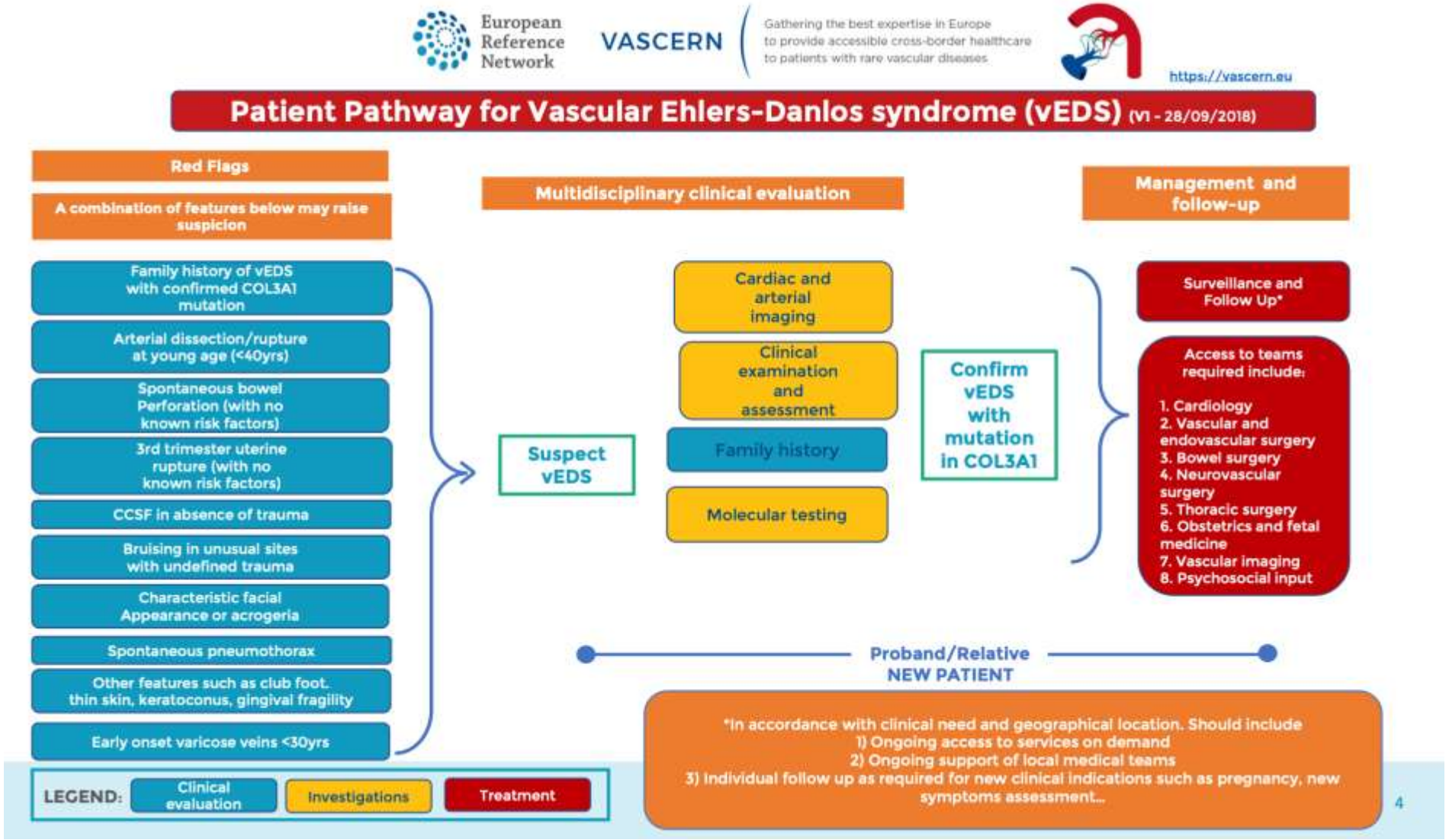
## Marfan syndrome

| System/Concern | Evaluation | Comment |
|---|---|---|
| **Constitutional** | Measurement of length/height | To assess for tall stature & growth [1] |
| **Eyes** | Ophthalmologic eval, ideally by ophthalmologist w/expertise in MFS | To incl:<br>• Slit lamp exam through maximally dilated pupil for evidence of lens subluxation<br>• Refraction, esp in young children at risk for amblyopia<br>• Assessment for glaucoma & cataract |
| **Musculoskeletal** | Clinical assessment for skeletal manifestations that may require immediate attn of an orthopedist (e.g., severe scoliosis) | |
| **Dental** | Assessment by dentist | For dental crowding & palatal issues |
| **Cardiovascular** | Echocardiography [2] | Esp aortic root measurements, which must be based on consideration of normal values for age & body size; click here for a calculator. |
| **Neurologic** | Consider spinal MRI to assess for dural ectasia. | In those w/low back pain, proximal leg pain, weakness & numbness above knee & genital/rectal pain |
| **Skin** | Clinical assessment for hernias | |
| **Respiratory** | Consider chest radiograph to assess for pneumothorax. | In those w/pain in chest, dyspnea, chest tightness, &/or cyanosis |

## Loeys Dietz syndrome

| System/Concern | Evaluation | Frequency |
|---|---|---|
| **Cardiovascular** | Echocardiography to monitor status of aortic root & ascending aorta | At least annually or more often per cardiologist |
| | MRA or CTA w/3D reconstruction from head to pelvis to identify arterial aneurysms & arterial tortuosity throughout the arterial tree | • At least every other year, or more frequently per cardiologist<br>• More frequent imaging may be indicated based on genotype, family history, absolute vessel size or growth rate, or vascular pathology. |
| **Pectus deformity** | Clinical assessment | At each visit or as needed |
| **Joint manifestations** | | |
| **Cervical spine instability** | Follow-up imaging | Per orthopedist |
| **Scoliosis** | Clinical &/or radiographic assessment | |
| ***Pes planus*** | Clinical assessment | At each visit or as needed |
| **Hernias** | Clinical assessment for hernias | At each visit or annually |
| **Allergic/ Inflammatory** | Assessment for clinical manifestations of asthma, food allergy, eczema, allergic rhinitis, &/or eosinophilic gastrointestinal disease | |
| **Ocular** | Eye exam by ophthalmologist w/expertise in connective tissue disorders incl:<br>• Assessment for refractive error<br>• Specific assessment for retinal detachment | Per ophthalmologist |

# Gestione comorbidità in forme sindromiche



# Gestione comorbidità

**CENTRO DI RIFERIMENTO REGIONALE (TOSCANA) PER LA SINDROME DI MARFAN E MALATTIE CORRELATE**

# Dati del nostro Centro

Azienda Ospedaliero Universitaria Careggi

Regione Toscana

European Reference Network VASCERN

## Attività

Il Centro afferisce alla SOD Malattie Aterotrombotiche e si occupa principalmente del trattamento delle seguenti patologie:

- sindrome di Marfan
- sindromi di Ehlers-Danlos
- osteogenesi imperfetta
- sindrome di Stickler
- ectopia della lente
- aneurisma aortico toracico
- aneurisma aortico addominale
- sindrome di Loeys Dietz
- sindrome della tortuosità dei vasi
- sindrome MASS
- sindrome del prolasso della valvola mitrale
- valvola aortica bicuspide
- cutis laxa
- omocistinuria

Casi totali (indice e familiari) del centro: circa 1500

Inseriti nel registro regionale RTMR 602 casi nell'ambito delle Malattie vascolari multisistemiche

- 499 MFS
- 67 EDS di cui 3 vEDS
- 11 LDS
- 2 sindrome di Stickler
- 2 Omocistinurici
- 10 sindromi malformative congenite
- 11 Altre condizioni

INTRODUCTION
EXPERTS +
PATIENT REPRESENTATION +
RARE DISEASE WORKING GROUPS
TRANSVERSAL WORKING GROUPS
NETWORK MAP

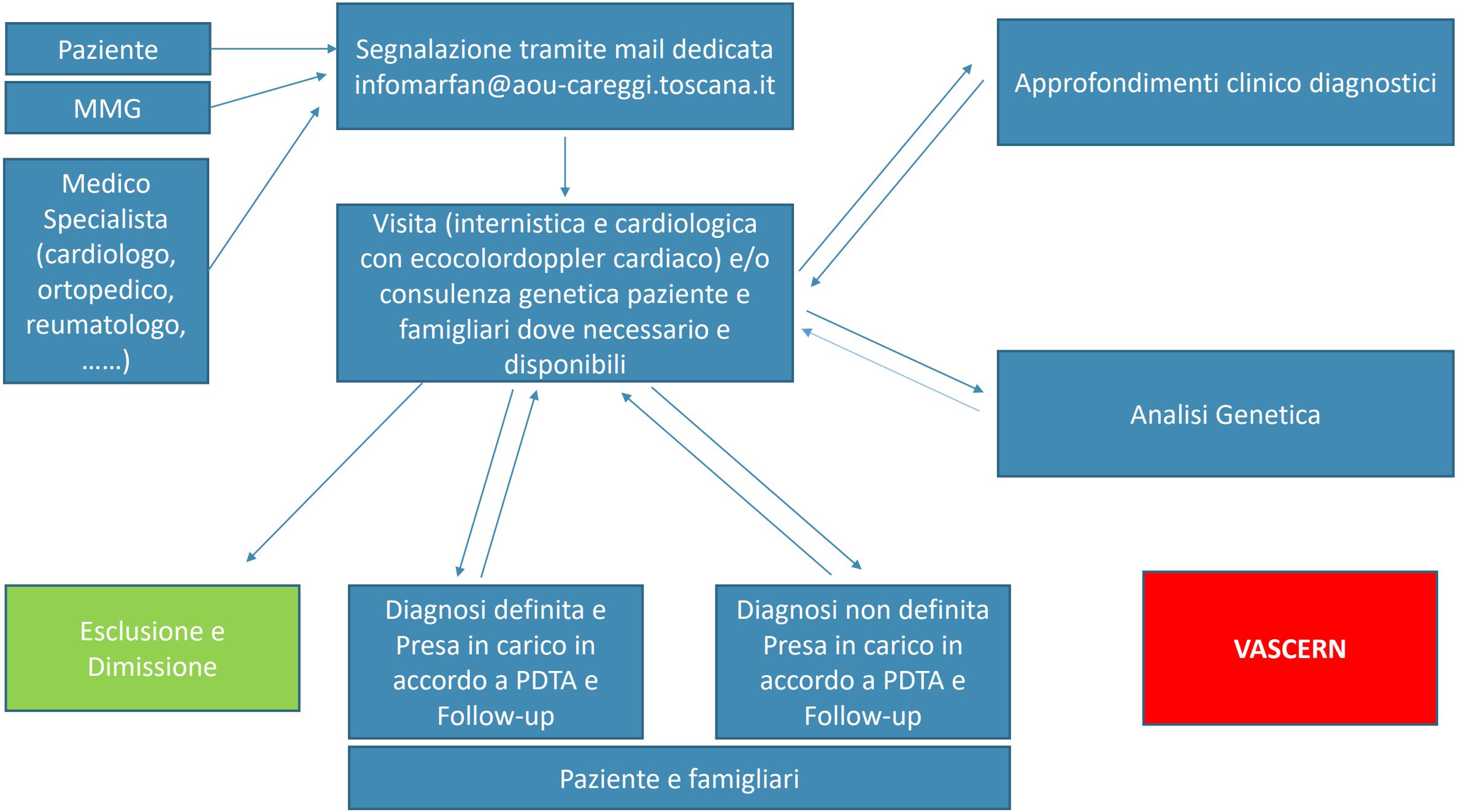
# Network Map

**Scheda percorso Diagnostico, Terapeutico e Assistenziale (PDTA) relativo a:**

**---------Sindrome di Marfan / RN1320 ---------**

*(Denominazione/codice di esenzione come da DGR 962 del 2017 (DPCM 12/01/2017)*
*vedi www.malattierare.toscana.it)*

# CENTRO DI RIFERIMENTO REGIONALE (TOSCANA) PER LA SINDROME DI MARFAN E MALATTIE CORRELATE



# Vasi di medio calibro

Azienda Ospedaliero Universitaria Careggi

**Mod. B11**
Vers_20160118

**PROTOCOLLO**

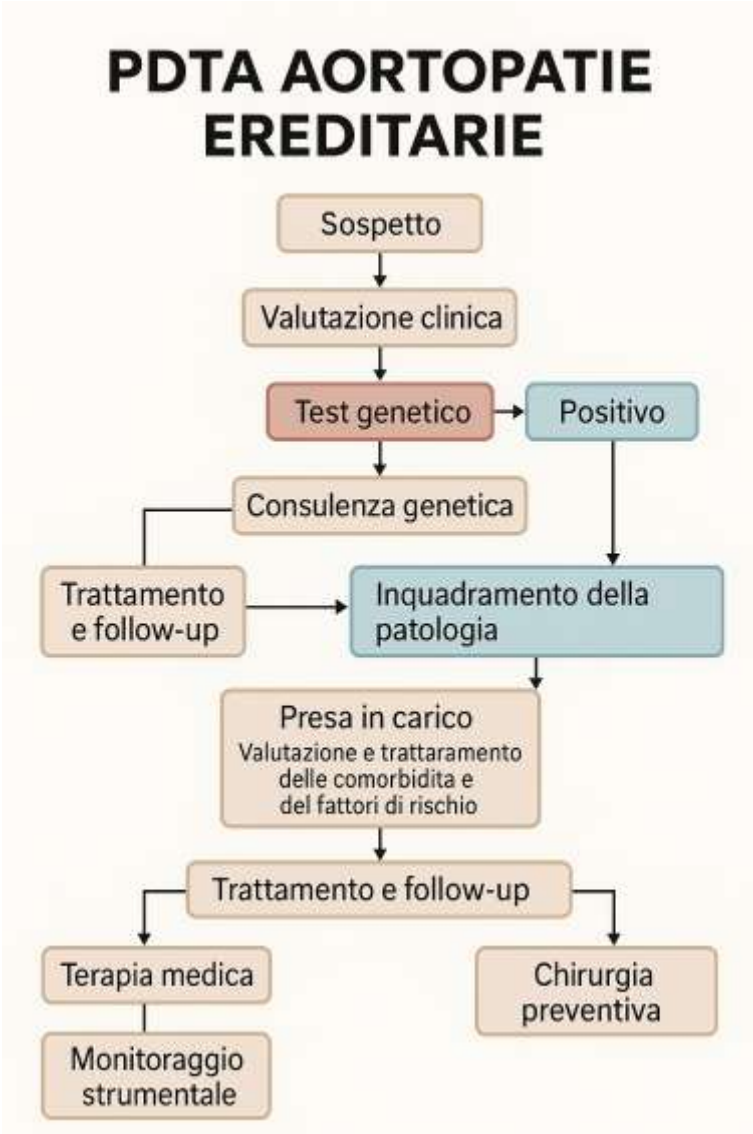
**STUDIO OSSERVAZIONALE**

| | |
|---|---|
| **Titolo dello Studio:** | SPontaneous coRonary artery dIssectioN: is time for a reproduCible and univoque diagnostic procESS? The PRINCESS trial |
| **Codice del Protocollo:** | |
| **Versione del Protocollo:** | I |
| **Data:** | 30/04/2024 |
| **Promotore:** | *Dipartimento di Medicina Sperimentale e Clinica* |
| **Centro Coordinatore:** | SOD Malattie Aterotrombotiche, DAI CardioToracoVascolare, AOU Careggi |

# Conclusioni

PDTA: strumento per

- Sensibilizzare al sospetto di HTAD
- Ottimizzare e uniformare il percorso diagnostico
- Facilitare la gestione mutidisciplinare dei pazienti



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Dr.ssa Angela Rogolino
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