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Genetic Aortopathy

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Learning Objectives

- By the end of this seminar, attendees will be able to:
  - list indications for genetic testing in people who have aortic disease.
  - differentiate between syndromic aortopathies and Familial Thoracic Aortic Aneurysm and Dissection conditions.
  - describe how genetic testing results can modify vascular screening, pharmacologic management, and surgical thresholds for people with aortic disease.

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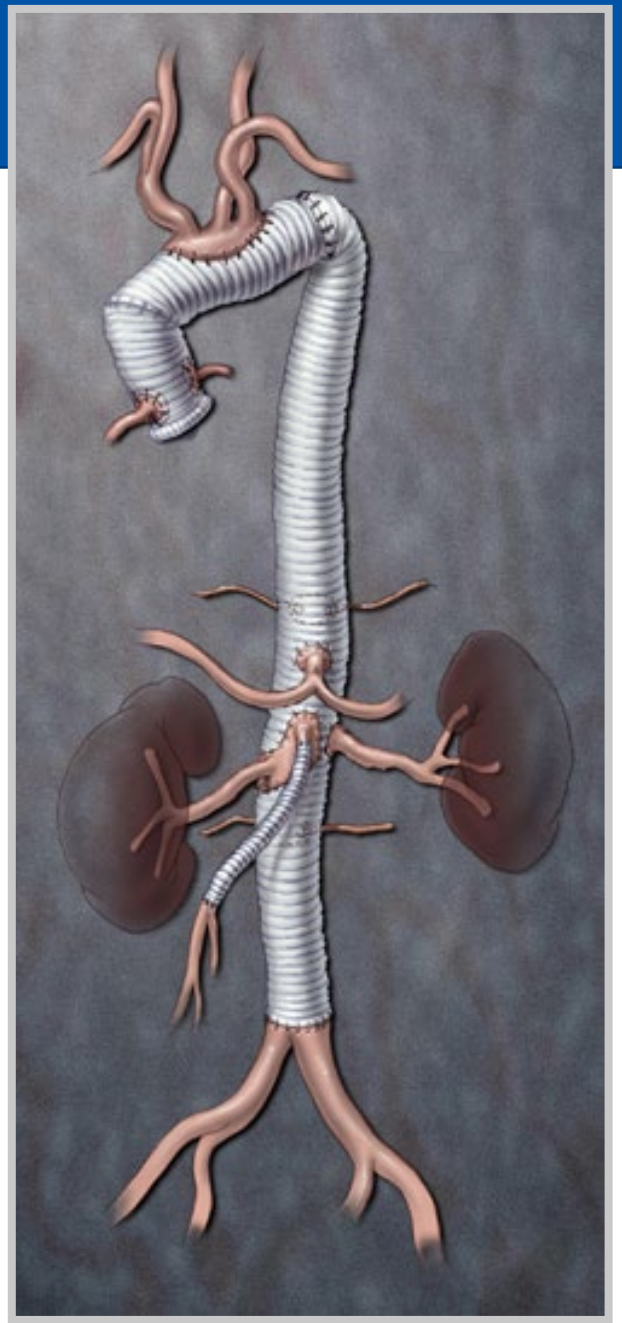
Introduction to Genetic Aortopathy

Definition

Aortopathy:

“disease of the aorta”



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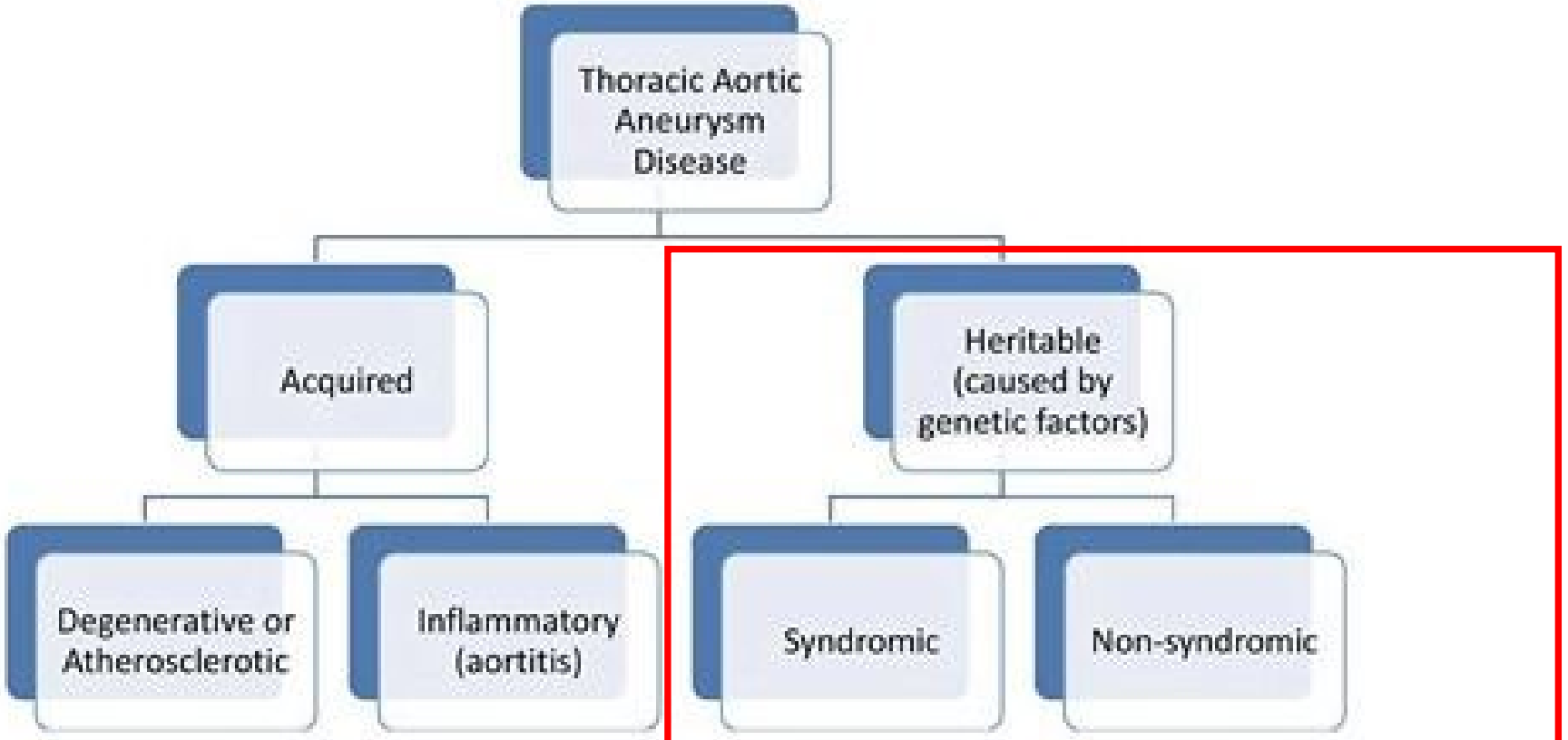
Classification



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Learning Objective 1:
Indications for genetic testing

Indications for Genetic Testing

- TAD and syndromic features of Marfan syndrome, Loeys-Dietz syndrome, or vascular Ehlers-Danlos syndrome
- Family history of either TAD or peripheral/intracranial aneurysms in a first or second-degree relative
- TAD presenting at age <60 years of age

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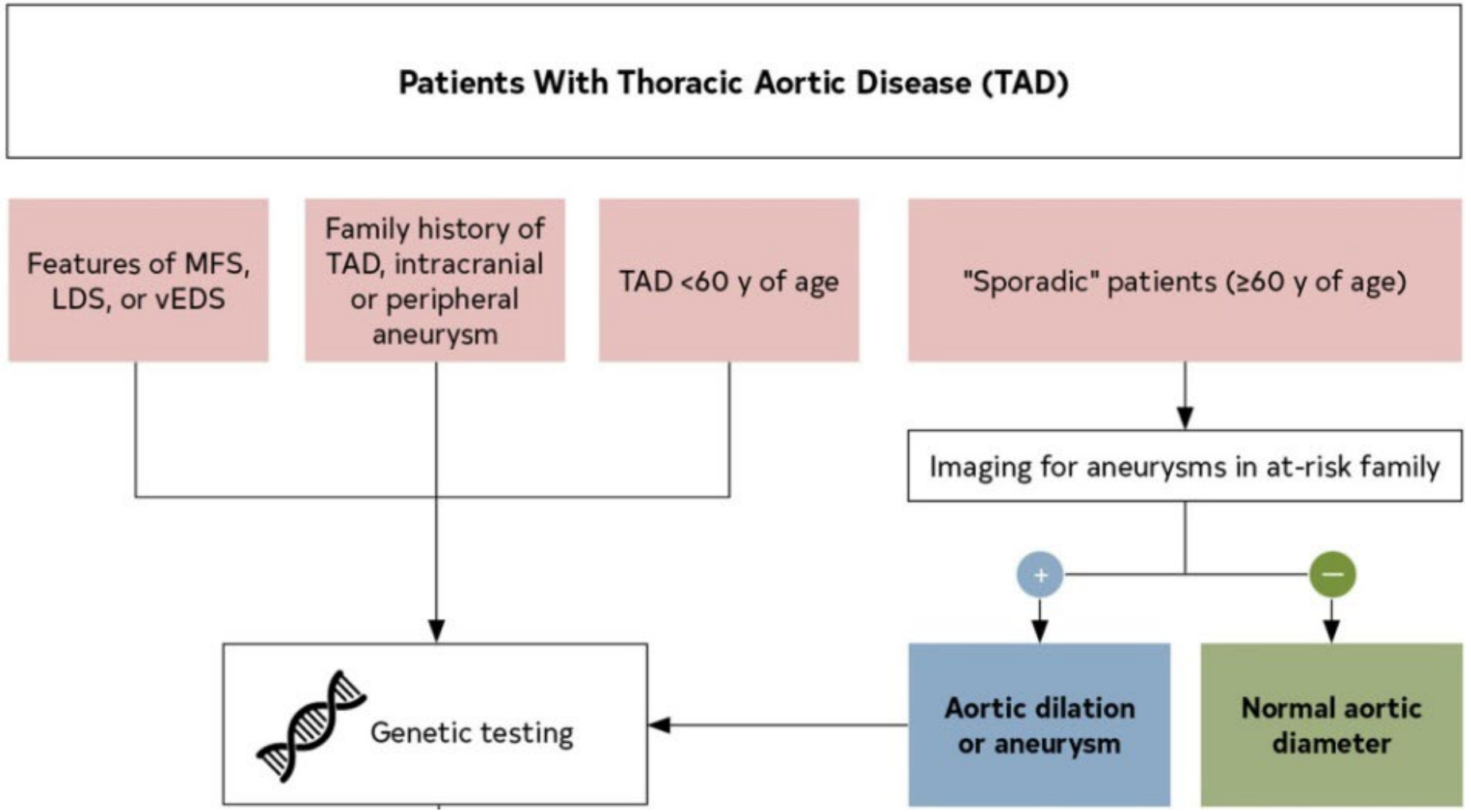
2022 ACC/AHA Guideline for the Diagnosis and Management of Aortic Disease.
J Am Coll Cardiol 2022 Dec 13;80(24):e223-e393. doi: 10.1016/j. jacc. 2022.08.004.

2022 ACC/AHA Guidelines for the Diagnosis and Management of Aortic Disease (Figure 17)



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2022 ACC/AHA Guideline for the Diagnosis and Management of Aortic Disease. J Am Coll Cardiol 2022 Dec 13;80(24):e223-e393. doi: 10.1016/j. jacc. 2022.08.004.

Genetic Testing Options

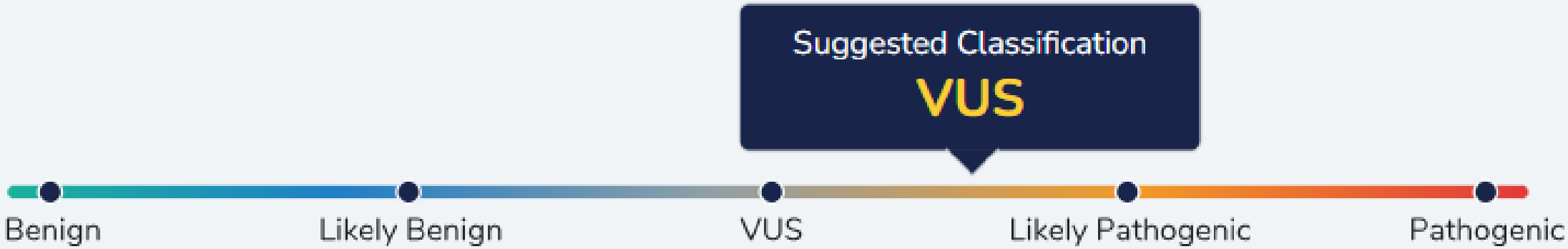
- Physician-ordered vs direct to consumer
- Commercial vendors vs university labs
- Insurance vs self-pay
- Single gene vs gene panels

Genetic Testing Risks

- Possible exclusion from military participation
- Possible denial of future life insurance applications
- Types of results:
  - Positive
  - Negative
  - Variants of Uncertain Significance

Variants of Uncertain Significance

- Ordering provider must ensure that patients have access to an individual who can appropriately interpret results and perform necessary follow up (such as a genetic counselor)
- There is strict criteria to re-classify a variant as either benign, likely benign, pathogenic or likely pathogenic.



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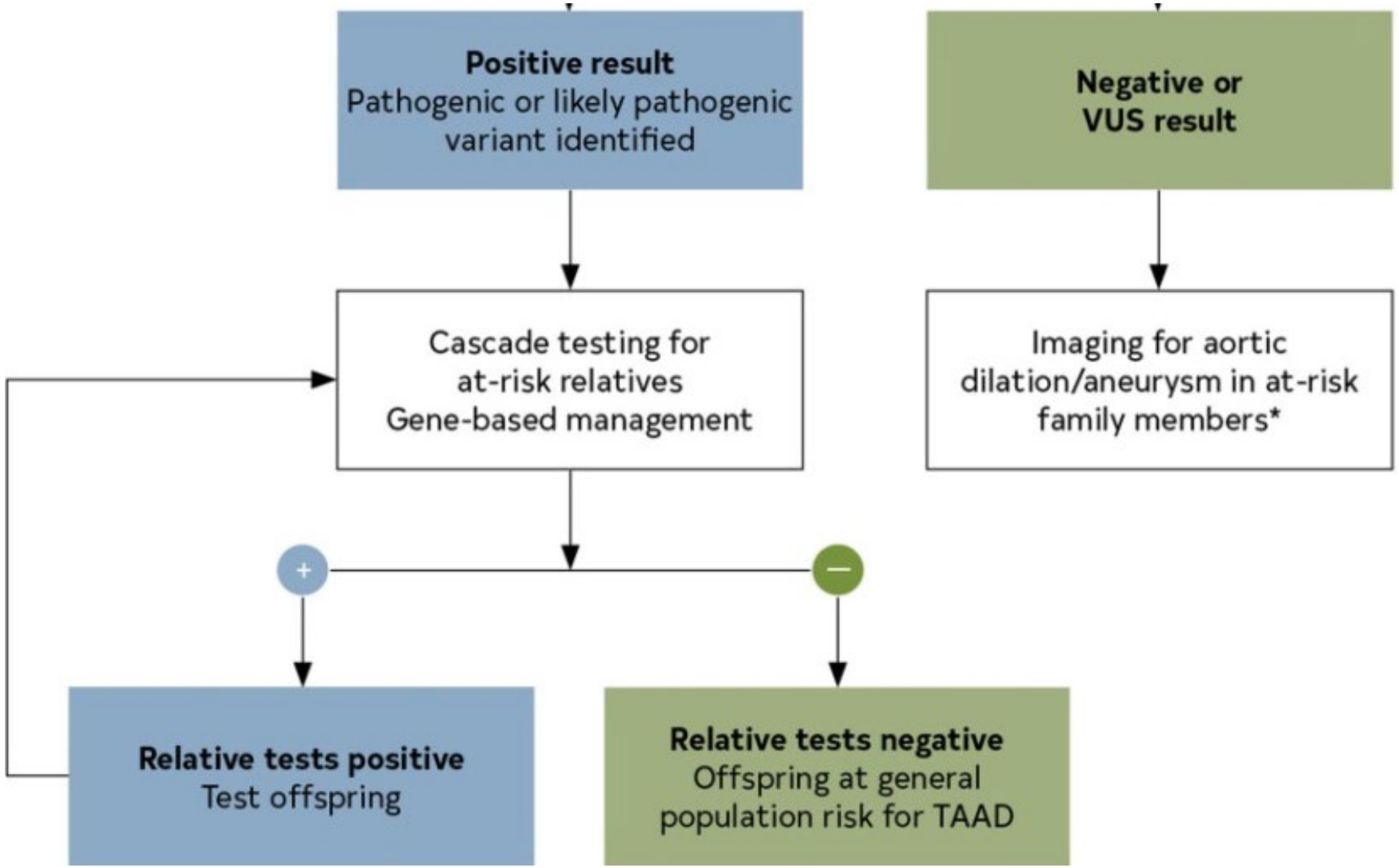
Genetic Result Management Sequence



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2022 ACC/AHA Guideline for the Diagnosis and Management of Aortic Disease.
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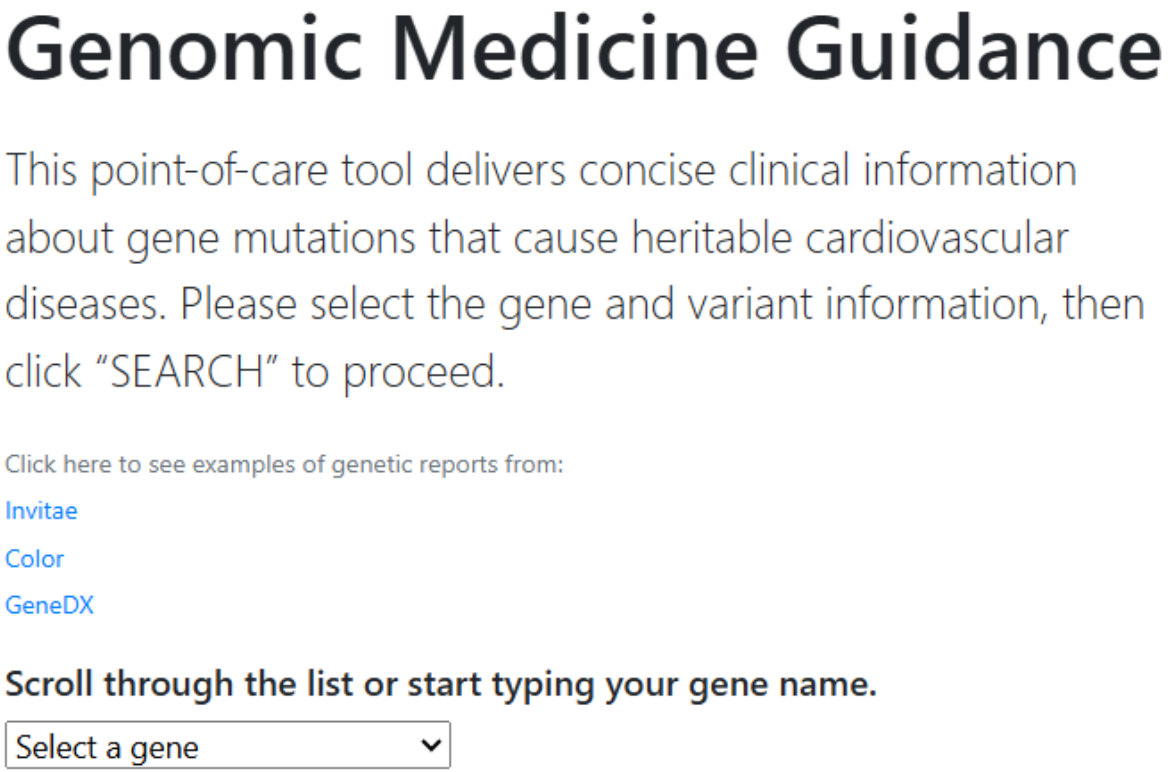
Variant Interpretation App



This app contains data on the 13 most frequent TAAD genes as well as 2,286 pathogenic mutations that cause TAAD.

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https://redcap.uth.tmc.edu/plugins/HTAD_copy/index825.php

Family Implications

- In all individuals with positive history of HTAD or pathogenic variant on genetic testing, screen all first-degree relatives (siblings, children, and parents) with echocardiogram!

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Learning Objective 2:
syndromic vs non-syndromic aortopathies

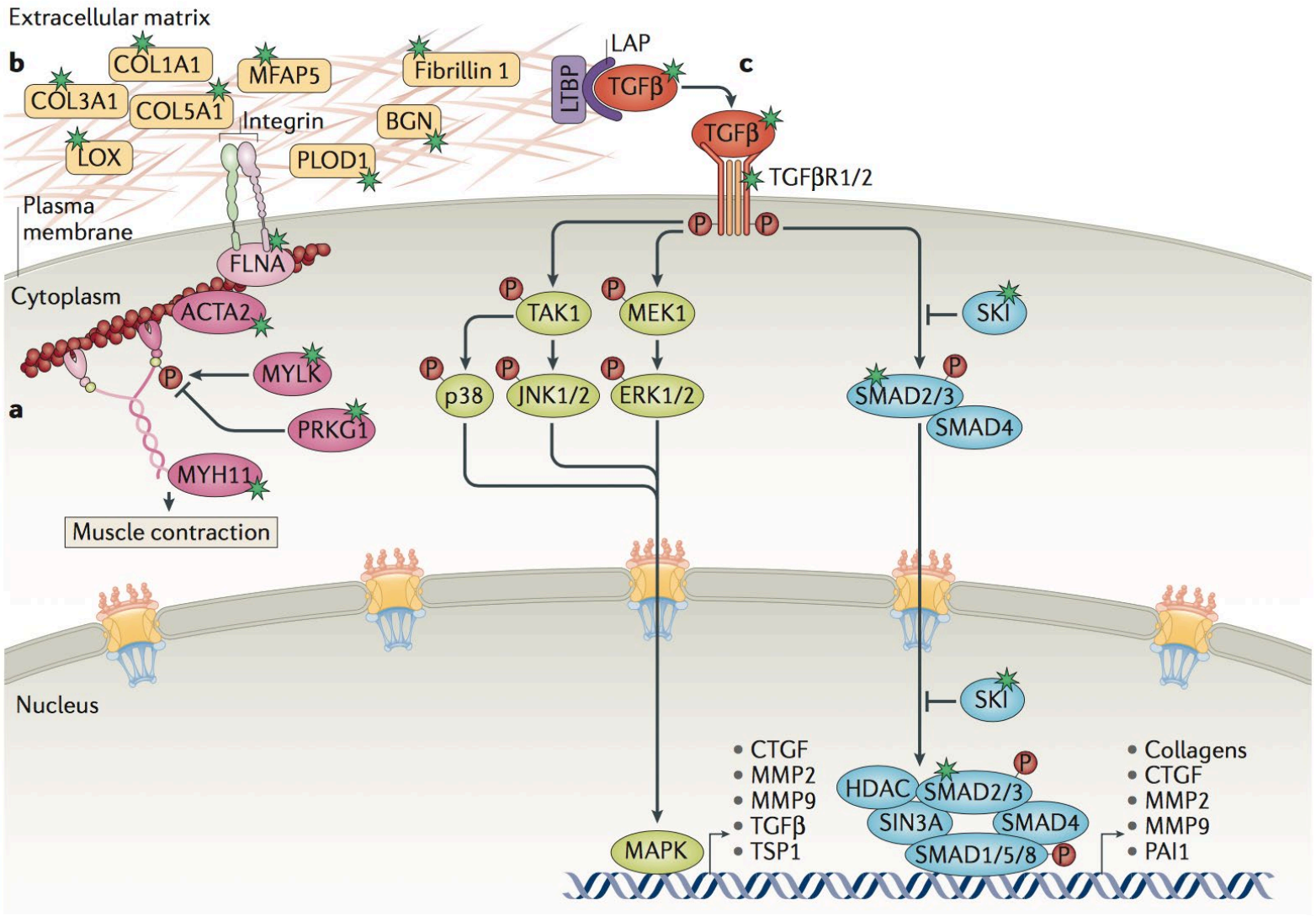
Causes of Syndromic vs Non-Syndromic HTAD

- **Syndromic HTAD**
  - Marfan syndrome (FBN1)
  - Loeys Dietz syndromes (TGFBR1, TGFBR2, SMAD3, TGFB2, TGFB3)
  - Vascular Ehlers-Danlos syndrome (COL3A1)
  - Arterial Tortuosity Syndrome (SLC2A10)
  - Shprintzen-Goldberg Syndrome (SKI)
  - LOX-related TAA (LOX)
  - Smooth Muscle Dysfunction Syndrome (ACTA2)
- **Non-Syndromic**
  - ACTA2
  - MYH11
  - MYLK
  - PRKG1
  - MAT2A
  - MFAP5
  - FOXE3
  - THSD4

2022 ACC/AHA Guideline for the Diagnosis and Management of Aortic Disease.
J Am Coll Cardiol 2022 Dec 13;80(24):e223-e393. doi: 10.1016/j. jacc. 2022.08.004.

Signalling Pathways involved in HTAD

Genes known to cause HTAD are denoted with green asterisk



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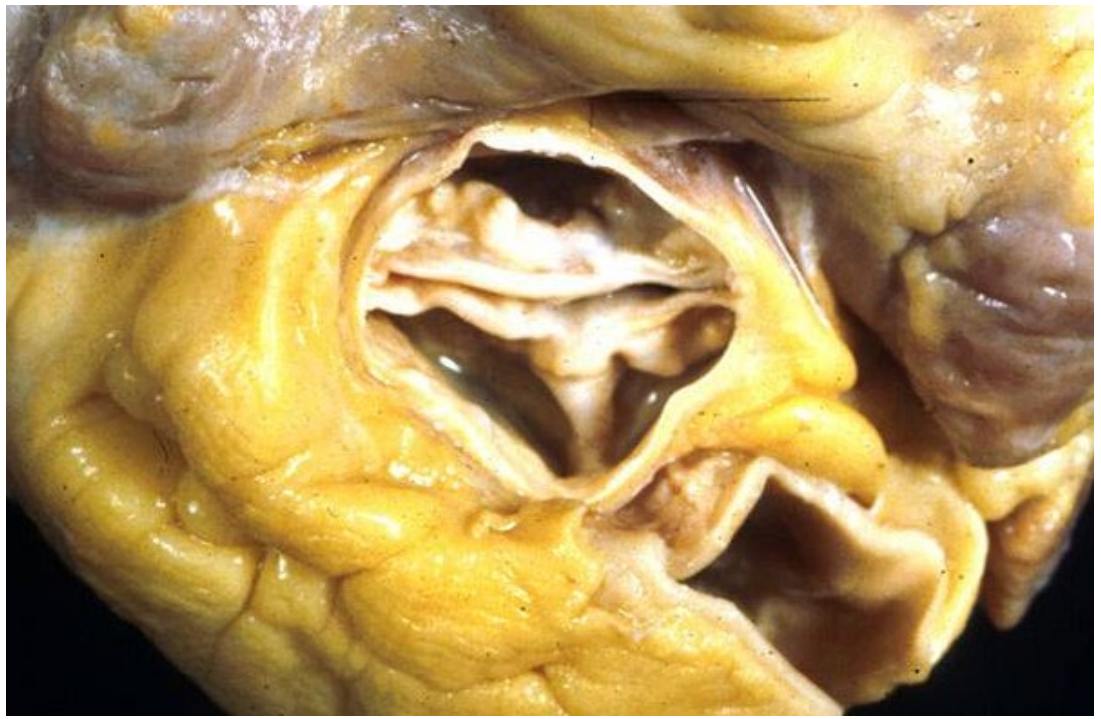
Verstraeten, Luyckx, and Loeys, Nature Reviews: Cardiology. Volume 14, April 2017

Bicuspid Aortic Valve

- BAV is a risk factor for developing ascending aortic aneurysm.
- BAV causes hemodynamic flow disturbances, resulting in increased wall shear stress in the ascending aorta.
- Increasing evidence for genes that independently cause BAV.

Bicuspid Aortic Valve



Pathology specimen photos courtesy of William O'Connor, MD, Department of Pathology, University of Kentucky

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Syndromic HTAD

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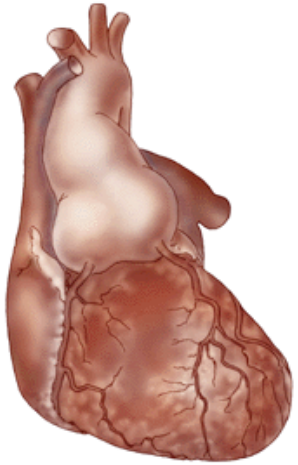
Marfan Syndrome



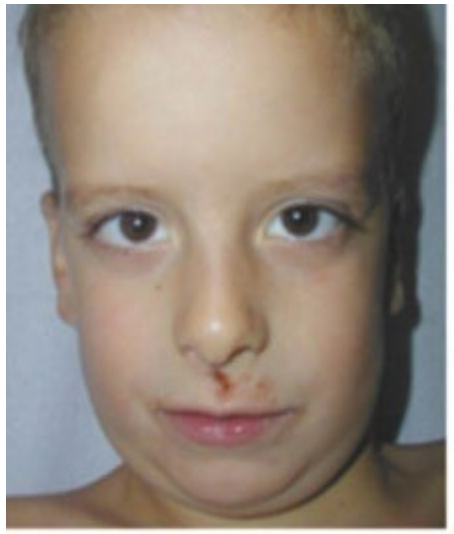
University of Kentucky

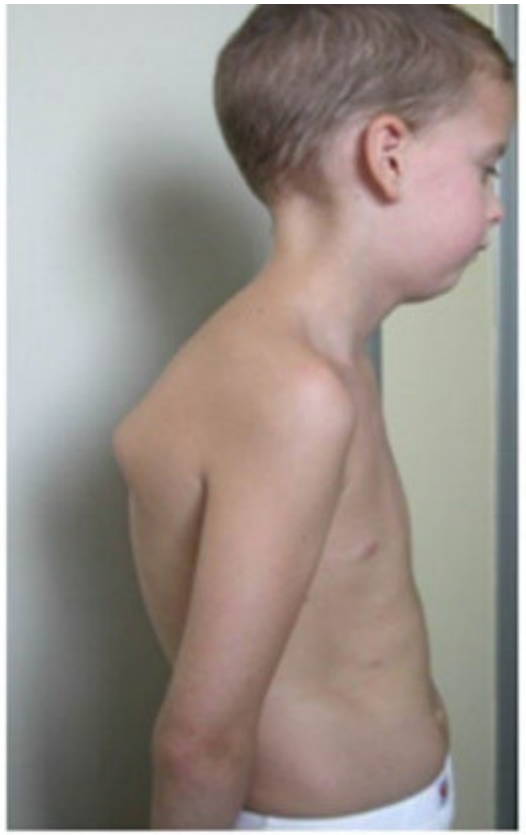
Pictures provided courtesy of the National Marfan Foundation

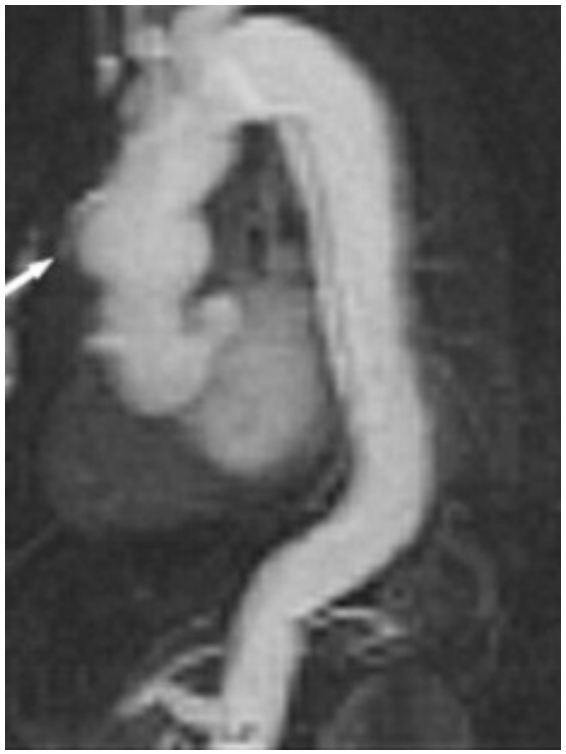
Diagnosis of Marfan in Absence of Family History

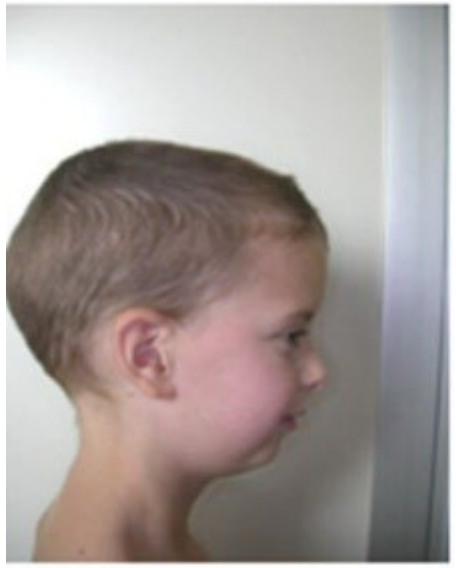
- Ao and EL
- Ao and systemic score
- Ao and FBN1 mutation
- EL and FBN1 mutation

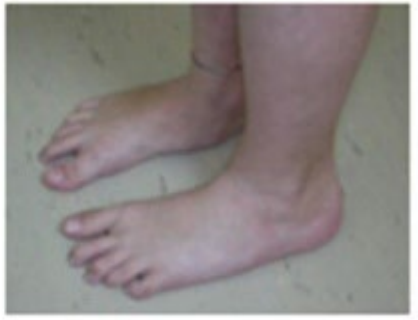
Loeys-Dietz Syndrome

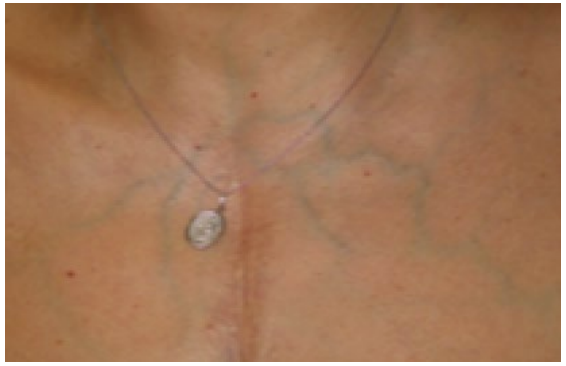












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Diagnosis of Loeys-Dietz Syndrome

- Requires genetic testing to identify the specific gene that causes each subtype
  - Type 1: TGFBR1
  - Type 2: TGFBR2
  - Type 3: SMAD3
  - Type 4: TGFB2
  - Type 5: TGFB3
- Subtype diagnosis will affect surgical threshold for aortic repair
- Each subtype has a unique natural history

Vascular Ehlers-Danlos Syndrome (COL3A1)

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Diagnosis of Vascular EDS (EDS type 4)

- Genetic basis: COL3A1 (rarely can be COL1A1)
- Minimal criteria suggestive of vEDS:
  - Any of the following:
    - FH of vEDS
    - Arterial rupture or dissection in individuals less than 40 years of age
    - Unexplained sigmoid colon rupture
    - Spontaneous pneumothorax in the presence of other features consistent with vEDS

Variable Expressivity

Phenotype features can vary greatly between individuals, even in the same family with the same gene mutation.

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Learning Objective 3: impact on medical and surgical management

REVIEW ARTICLE | Originally Published 12 August 2024 |

Cardiovascular Management of Aortopathy in Children: A Scientific Statement From the American Heart Association

Shaine A. Morris, MD, MPH, Vice Chair, Jonathan N. Flyer, MD, Anji T. Yetman, MD, Emilio Quezada, MD, Elizabeth S. Cappella, APRN-NP, Harry C. Dietz, MD, Dianna M. Milewicz, MD, PhD, Maral Ouzounian, MD, PhD, Christina M. Rigelsky, MS, CGC, Seda Tierney, MD, FAHA, and Ronald V. Lacro, MD, Chair on behalf of the American Heart Association Council on Lifelong Congenital Heart Disease and Heart Health in the Young (Young Hearts); Council on Cardiovascular and Stroke Nursing; Council on Peripheral Vascular Disease; Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation; and Council on Cardiovascular Surgery and Anesthesia | AUTHOR INFO & AFFILIATIONS

Circulation • Volume 150, Number 11 • https://doi.org/10.1161/CIR.0000000000001265

Vascular Imaging Surveillance

- Pediatric Imaging Guidelines

Color code	
	Every 12–24 mo
	Every 12–18 mo
	Every 6–12 mo
	Every 3–6 mo

Characteristics	Degree of aortic root or ascending dilation			
	None	Mild	Moderate	Severe
Age <16 y (*Z* score)	<2	≥2 and <3.5	≥3.5 and <5	≥5
Age ≥16 y (maximum dimension), cm	<3.5	≥3.5 and <4	≥4 and <4.5	≥4.5
Classic Marfan syndrome				
Early-onset Marfan syndrome	Imaging is driven by assessment of the atrioventricular valves, ventricular size, and function as much as by aortic dimensions; therefore, imaging frequency typically is every 1–3 mo, but may extend to every 6 mo with stable disease			
TGFBR1, *TGFBR2*			*	*
TGFB2, *TGFB3*, *SMAD2*				*†
SMAD3	‡			*

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Morris et al, Circulation 2024; 150(11):e228-e254. PMID 39129620.

Full List of Current Conditions

Characteristics	Degree of aortic root or ascending dilation			
	None	Mild	Moderate	Severe
Age <16 y (*Z* score)	<2	≥2 and <3.5	≥3.5 and <5	≥5
Age ≥16 y (maximum dimension), cm	<3.5	≥3.5 and <4	≥4 and <4.5	≥4.5
Classic Marfan syndrome				
Early-onset Marfan syndrome	Imaging is driven by assessment of the atrioventricular valves, ventricular size, and function as much as by aortic dimensions; therefore, imaging frequency typically is every 1–3 mo, but may extend to every 6 mo with stable disease			
TGFBR1, *TGFBR2*			*	*
TGFB2, *TGFB3*, *SMAD2*				*†
SMAD3	‡			*
Vascular EDS				*
Classic EDS	§			
ACTA2 (not R179)				*
ACTA2 (R179)			*	*
MYH11, *LOX*				*
MYLK	‡			
PRKG1	‖	‖	*‖	*‖
FLNA				
EFEMP2, arterial tortuosity syndrome	Rare; imaging is driven by specific cardiovascular lesions. More severe stenoses or dilation should be followed closely			
Bicuspid aortic valve (more frequent with AS or AR)	‡			
Dilated aorta or suspected HTAD with negative genetic testing and no other diagnosis	‡			
TGA, TAC, TOF, PA-VSD, Fontan	Based on underlying congenital heart disease			

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Morris et al, Circulation 2024; 150(11):e228-e254. PMID 39129620.

Pharmacologic Management

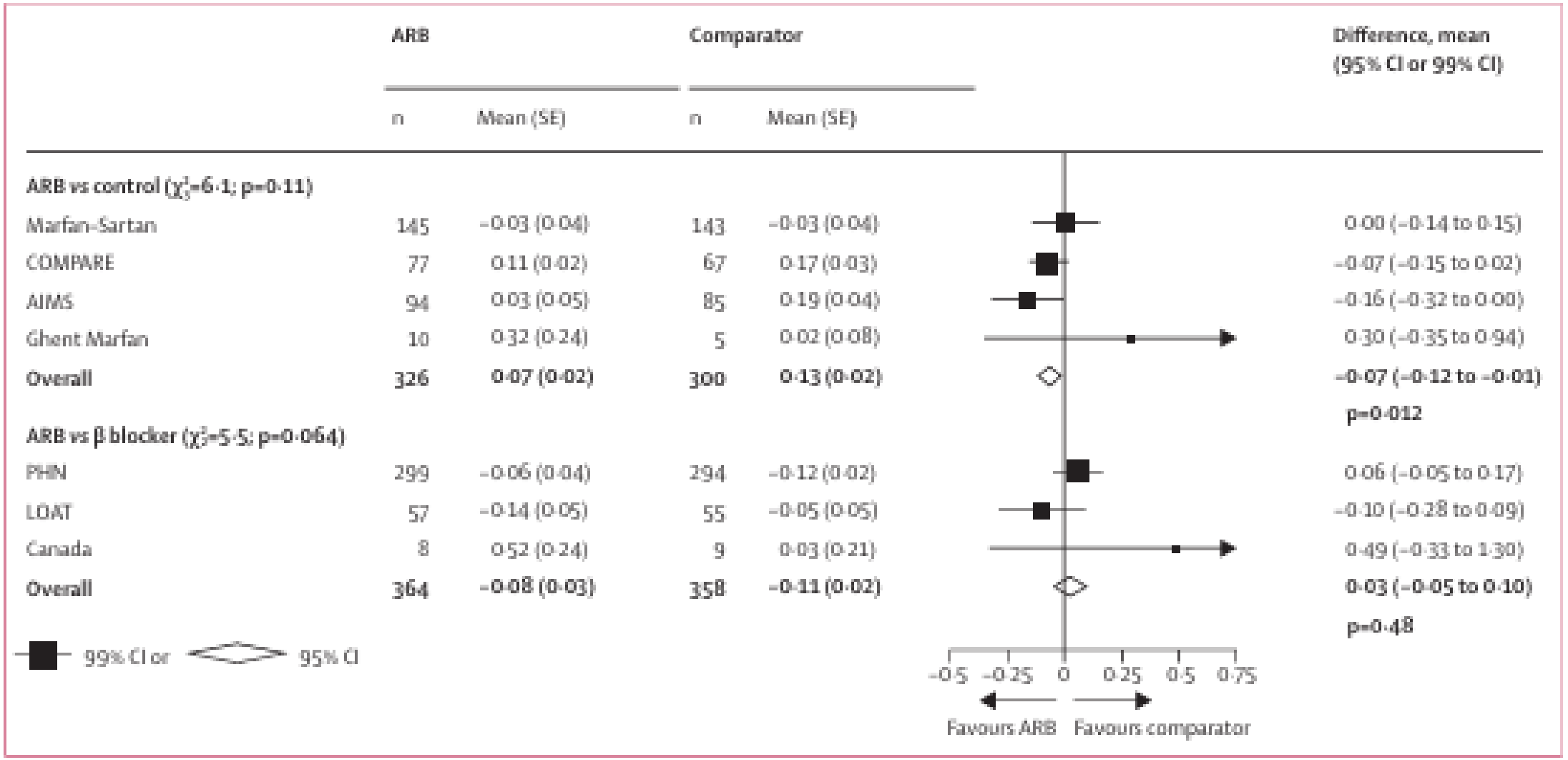
- ARB + beta-blockers

Angiotensin receptor blockers and β blockers in Marfan syndrome: an individual patient data meta-analysis of randomised trials

Alex Pitcher, Enti Spata, Jonathan Emberson, Kelly Davies, Heather Halls, Lisa Holland, Kate Wilson, Christina Reith, Anne H Child, Tim Clayton, Matthew Dodd, Marcus Flather, Xu Yu Jin, George Sandor, Maarten Groenink, Barbara Mulder, Julie De Backer, Arturo Evangelista, Alberto Forteza, Gisela Teixido-Turà, Catherine Boileau, Guillaume Jondeau, Olivier Milleron, Ronald V Lacro, Lynn A Sleeper, Hsin-Hui Chiu, Mei-Hwan Wu, Stefan Neubauer, Hugh Watkins, Hal Dietz, Colin Baigent, on behalf of The Marfan Treatment Trialists' Collaboration

Lancet 2022; 400: 822–31.

Lancet meta-analysis Figure 1



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Lancet 2022; 400: 822–31.

Condition-specific Medical Therapy

Characteristics	Degree of aortic root or ascending dilation			
	None	Mild	Moderate	Severe
Age <16 y (*Z* score)	<2	≥2 to <3.5	≥3.5 to <5	≥5
Age ≥16 y (maximum dimension), cm	<3.5	≥3.5 to <4	≥4 to <4.5	≥4.5
Marfan syndrome	*			
TGFBR1 or *TGFBR2*	*			
TGFB2, *TGFB3*, *SMAD3*, or *SMAD2*	*			
Vascular EDS	See section on Vascular Ehlers-Danlos Syndrome			
Classic EDS				
ACTA2 (not R179)				
ACTA2 R179	‡‡	‡	‡	‡
MYH11, *LOX*, *MYLK*				
PRKG1	†			
FLNA				
EFEMP2				
Arterial tortuosity syndrome		§	§	§
Bicuspid aortic valve‖			¶	¶
Dilated aorta or suspected HTAD with negative genetic testing and no other diagnosis		*		
TGA, TAC, TOF, PA-VSD, Fontan				#

	No medication
	Single therapy
	At least single therapy, consider dual therapy (if tolerated)
	Dual therapy (if tolerated)**

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Morris et al, Circulation 2024; 150(11):e228-e254. PMID 39129620.

Additional Pharmacologic Considerations

- **Avoid flouroquinolones** unless there is no other option: FDA issued warning of two fold risk of aortic aneurysm and dissection.
- **Calcium Channel Blockers** were found to accelerate aneurysm expansion, rupture and premature lethality in Marfan mice.
- **Angiotensin Receptor Blockers** were found to dramatically slow aortic root growth in children with Marfan syndrome who previously had rapid aortic root growth.

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Surgical Thresholds: Adults

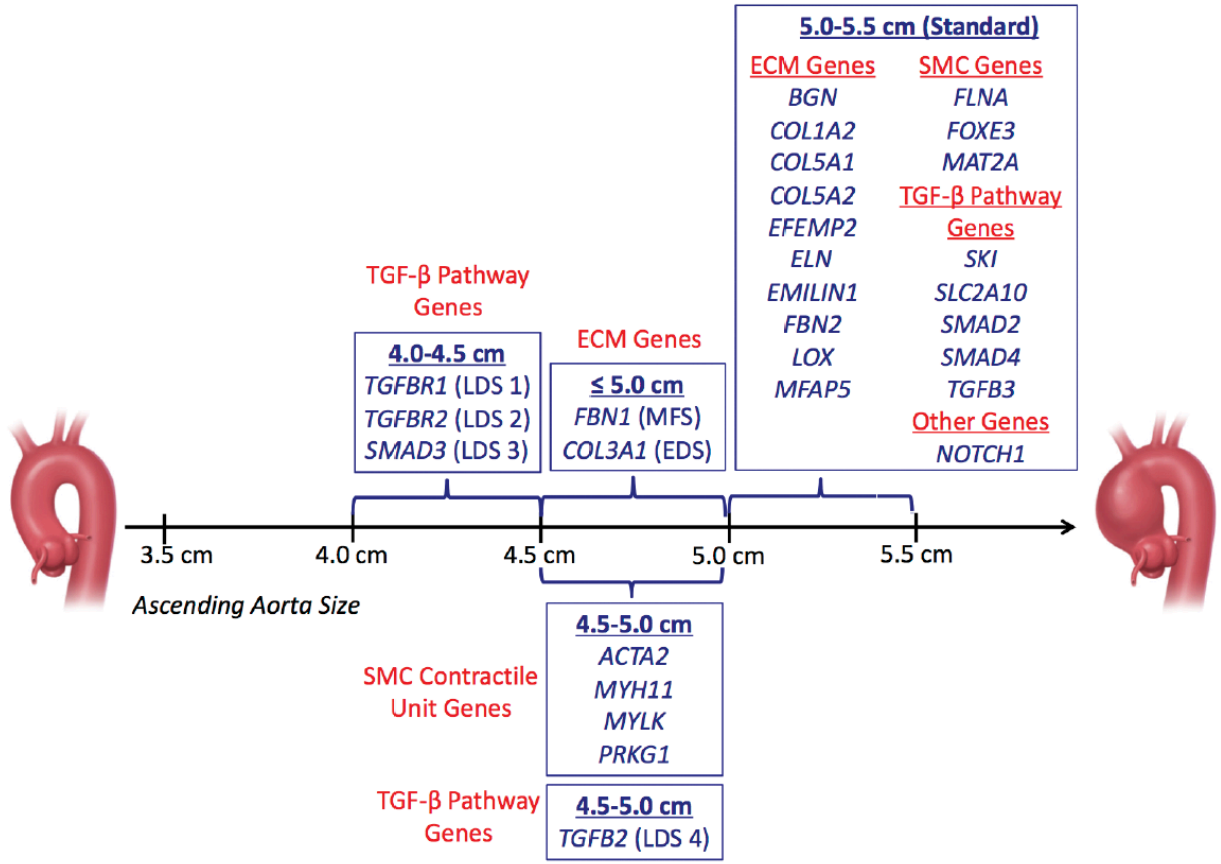

Figure 1. Simplified schematic illustration of ascending aorta dimensions for prophylactic surgical intervention divided by gene category: ECM genes, SMC contractile unit and metabolism genes, and TGF-β signaling pathway genes (data derived from Table 1). ECM, extracellular matrix; LDS, Loeys-Dietz syndrome; MFS, Marfan syndrome; SMC, smooth muscle cell; EDS, Ehlers-Danlos syndrome.

Condition-specific Surgical Thresholds: Pediatrics

	Standard risk
	High risk

Disorder or gene	Standard surgical threshold, maximum of aortic root or ascending aorta, cm	If high-risk features* are present, maximum of aortic root or ascending aorta, cm
Marfan syndrome	5.0 or maximum cross-sectional aortic area/height (cm^2/m) ≥10, age ≥16 y†	≥4.5 cm For early-onset Marfan syndrome with severe dilation (when aortic valve annulus ≥2): <2 y: 3.3–3.4 ≥2 and <5 y: 3.7–3.8 ≥5 y: 4
TGFBR1 or *TGFBR2*	≥4.5	When aortic valve annulus ≥2: <2 y: 3.3–3.4 ≥2 and <5 y: 3.7–3.8 ≥5 y: 4.0
TGFB2	≥4.5	≥4.5
TGFB3	≥5.0	≥5.0
SMAD3 or *SMAD2*	≥4.5	≥4.5
ACTA2	≥4.5‡	≥4.2‡ Insufficient data in young patients with severe dilation, as often seen in smooth muscle dysfunction syndrome (R179 variants); consider using early Marfan syndrome numbers
PKRG1	§	§
MYH11	≥4.5	≥4.5
MYLK	Although events occur without dilation, no events have been reported in childhood; if considering surgery, discuss with aortopathy expert	Although events occur without dilation, no events have been reported in childhood; if considering surgery, discuss with aortopathy expert

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Morris et al, Circulation 2024; 150(11):e228-e254. PMID 39129620.

Surgical Approach

- Endo vs open considerations
- Specific techniques recommended:
  - Endovascular Repair
    - Use soft catheters, avoid repeated sheath exchanges, lower the pressure in the power injector or utilize hand injections if possible to lower the risk of arterial tears and dissection.
  - Open Repair
    - Gentle retraction, padded clamps, pledgets

Surgical Considerations

- Document the diameter of the aorta at the time of dissection/rupture in affected family member.
  - recommended in the 2022 ACC/AHA Guideline for the Diagnosis and Management of Aortic Disease.

- In patient with HTAD and no identified genetic cause, consider early surgical repair if…
  - Family history of aortic dissection at an aortic diameter <5.0 cm.
  - Family history of unexplained sudden death at age <50
  - Rapid aortic growth (≥0.5 cm in 1 y or ≥0.3 cm/y in 2 consecutive years)

Risk Factor Modification

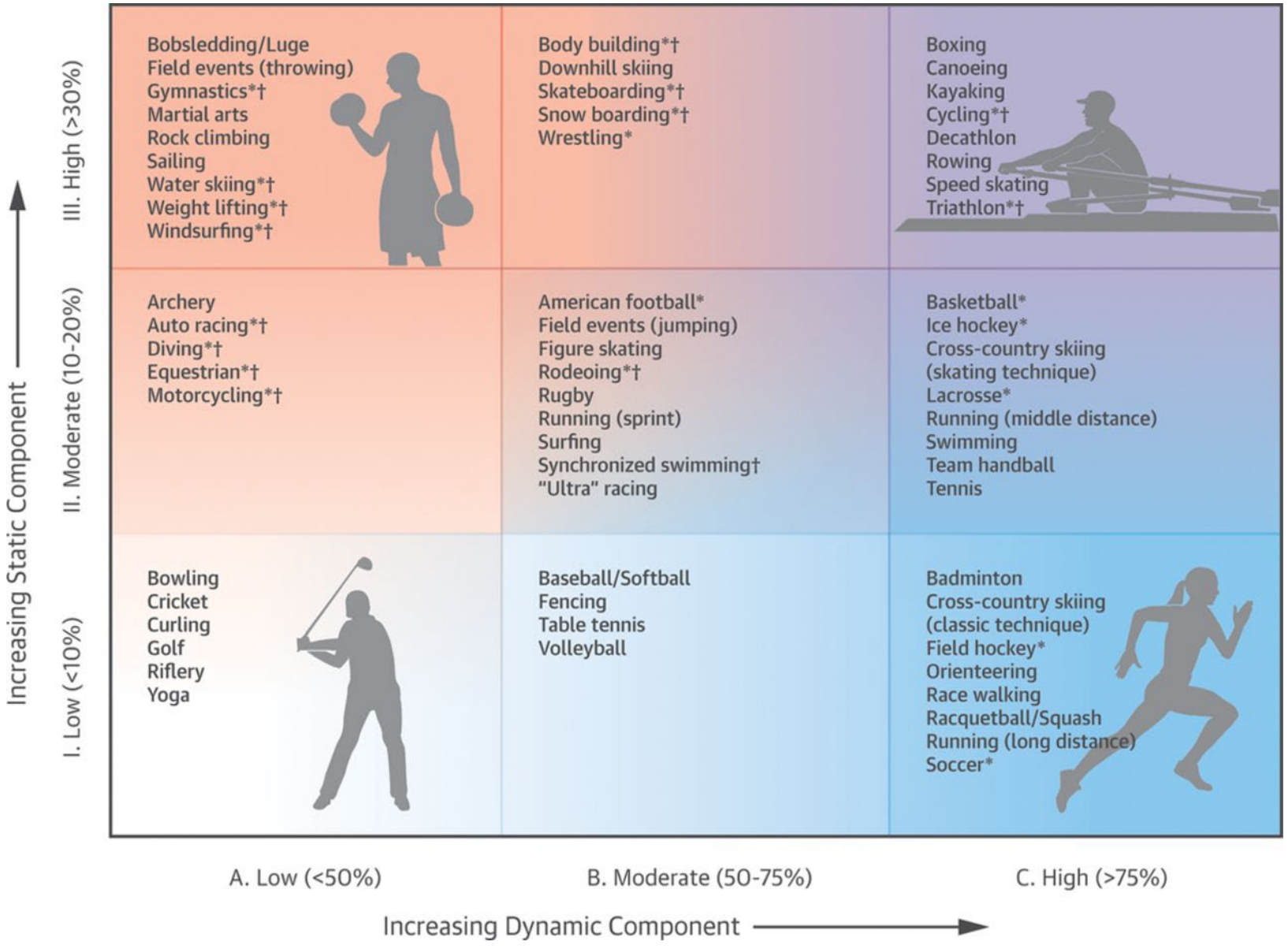
- Blood pressure
- Smoking Cessation
- Moderate aerobic exercise
  - benefits for the whole body, including mental health and social connections
  - could possibly be helpful for the aorta, depending on gene and type of exercise
    - Marfan mice that exercised had improved aortic wall structure and function, with optimal benefit at moderate intensity exercise (~60% of $V0_2$ max). Gibson C, et al. J Appl Physiol 2017.

Not all exercise is the same

- **Isometric (static) Exercise**
  - Muscle fibers contract without changes in length
  - Results in no muscle movement
  - Systemic blood vessels constrict
    - redirects flow to contracting muscles
  - Large increase in systolic BP (>300 mmHg during Valsalva maneuver)

- **Isotonic (dynamic) Exercise**
  - Muscle fiber length changes during exercise
  - Results in muscle movement
  - Systemic blood vessels dilate
  - Modest increase in mean BP

Classification of Sports



Levine AD, et al. JACC 2015;66:2350-3

Aortic Dissection Survivors: Activity Recommendations

- 314 survivors of acute aortic dissection surveyed regarding lifestyle modifications, exercise practice and emotional state. Response rate was 42%.
  - 32% with new-onset depression
  - 32% with new onset anxiety
  - 24% no longer engaged in any exercise
- Those who exercised routinely had less depression and lower BP.
- Cardiac rehabilitation has been successful in selected individuals after aortic dissection. Exercise prescriptions should be individualized and blood pressure monitored.

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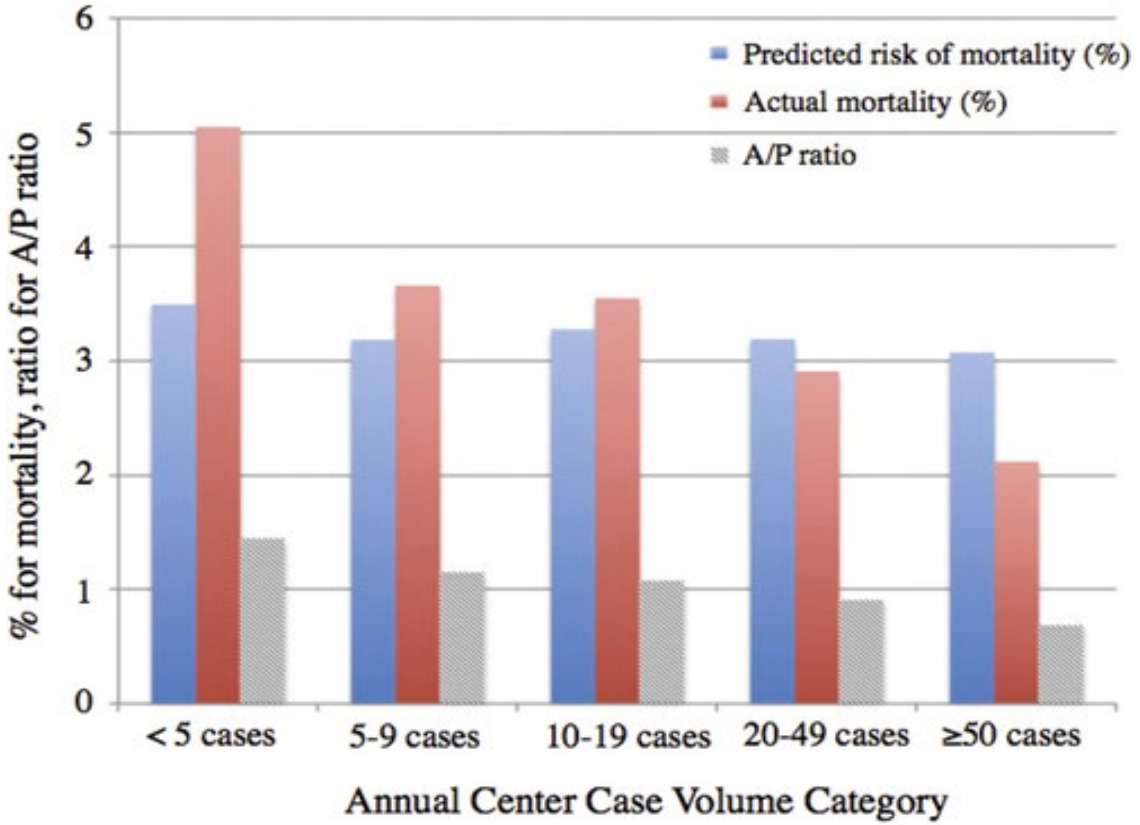
Chaddah A, Klein-Rodgers E, Braverman AC, et al. Clin Cardiol 2015;38:652-9.

Exercise Considerations Beyond the Aorta

Body System	
Ocular	Lens dislocation Retinal detachment
Cardiac	Cardiomyopathy Valvular disease Arrhythmia Anticoagulation (if mechanical valve)
Pulmonary	Spontaneous pneumothorax Restrictive lung disease
Musculoskeletal	Cervical spine instability Back, hip, foot pain

Aortic Centers

- Improved outcomes with a multidisciplinary expert team comprised of geneticists, cardiologists, cardiothoracic surgeons, vascular surgeons, pulmonologists, general surgeons, obstetricians.



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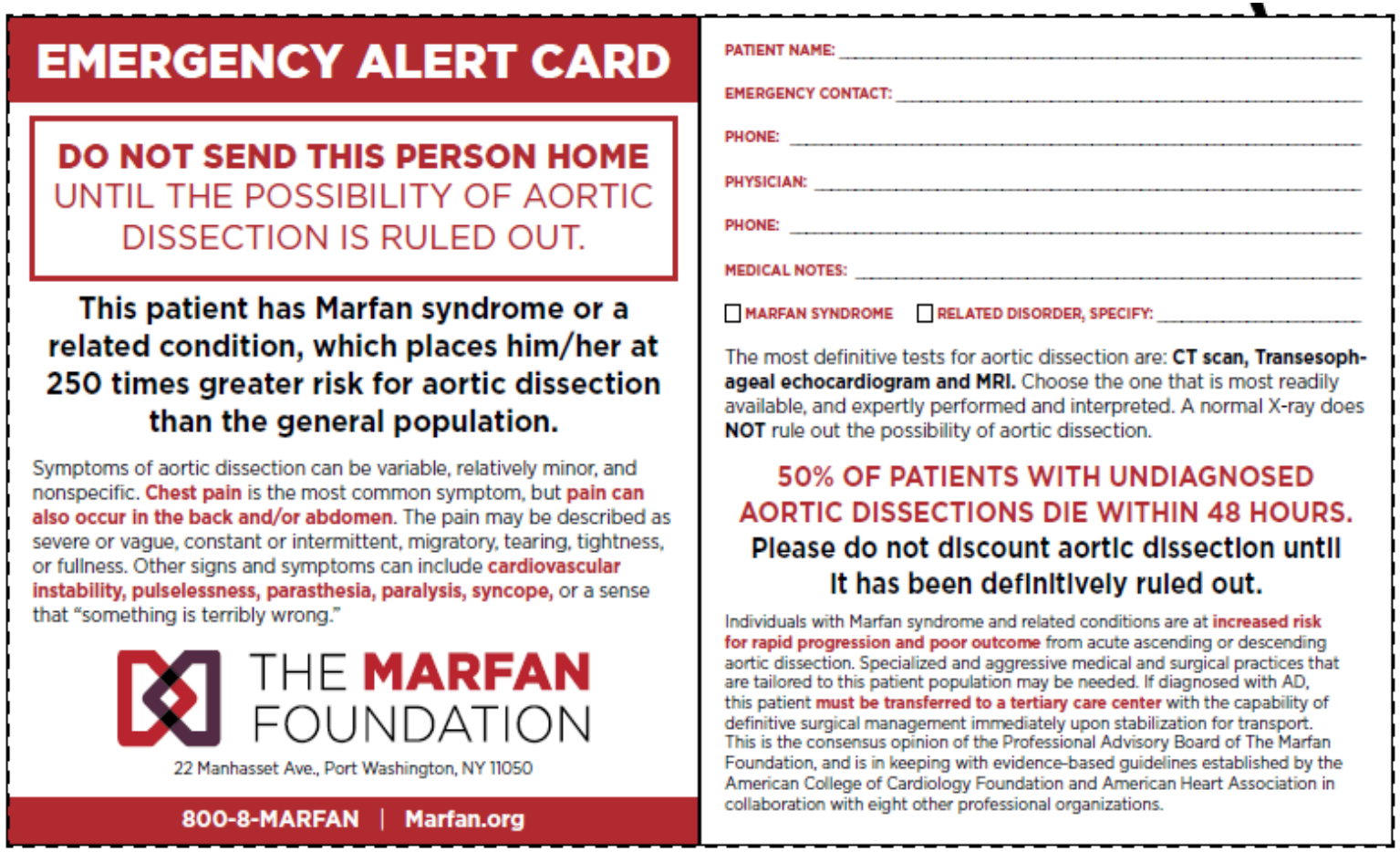
Emergency Preparedness



EMERGENCY ALERT CARD

DO NOT SEND THIS PERSON HOME
UNTIL THE POSSIBILITY OF AORTIC DISSECTION IS RULED OUT.

This patient has Marfan syndrome or a related condition, which places him/her at 250 times greater risk for aortic dissection than the general population.

Symptoms of aortic dissection can be variable, relatively minor, and nonspecific. **Chest pain** is the most common symptom, but **pain can also occur in the back and/or abdomen.** The pain may be described as severe or vague, constant or intermittent, migratory, tearing, tightness, or fullness. Other signs and symptoms can include **cardiovascular instability, pulselessness, parasthesia, paralysis, syncope,** or a sense that "something is terribly wrong."

THE MARFAN FOUNDATION

22 Manhasset Ave., Port Washington, NY 11050

800-8-MARFAN | Marfan.org

PATIENT NAME: _____

EMERGENCY CONTACT: _____

PHONE: _____

PHYSICIAN: _____

PHONE: _____

MEDICAL NOTES: _____

☐ MARFAN SYNDROME ☐ RELATED DISORDER, SPECIFY: _____

The most definitive tests for aortic dissection are: **CT scan, Transesophageal echocardiogram and MRI.** Choose the one that is most readily available, and expertly performed and interpreted. A normal X-ray does **NOT** rule out the possibility of aortic dissection.

50% OF PATIENTS WITH UNDIAGNOSED AORTIC DISSECTIONS DIE WITHIN 48 HOURS.
Please do not discount aortic dissection until it has been definitively ruled out.

Individuals with Marfan syndrome and related conditions are at **increased risk for rapid progression and poor outcome** from acute ascending or descending aortic dissection. Specialized and aggressive medical and surgical practices that are tailored to this patient population may be needed. If diagnosed with AD, this patient **must be transferred to a tertiary care center** with the capability of definitive surgical management immediately upon stabilization for transport. This is the consensus opinion of the Professional Advisory Board of The Marfan Foundation, and is in keeping with evidence-based guidelines established by the American College of Cardiology Foundation and American Heart Association in collaboration with eight other professional organizations.

https://marfan.org/wp-content/uploads/2021/04/MARFAN-EmergencyCard.pdf

Education Resources for Providers, Patients and Families

- Global community of healthcare professionals and scientists committed to advancing the understanding and care of all forms of genetic aortic vascular conditions.
  - Best Practices and Guidelines
  - Clinical Management Videos
  - Continuing Medical Education

UK HealthCare
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https://www.gentacalliance.org/

Clinical Research: Registries

- IRAD
- MAC
- CLARITY

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Clinical Research: Hip Pain in Marfan Syndrome

THE MARFAN FOUNDATION

THE MARFAN FOUNDATION AWARDS $675,000 IN NEW RESEARCH GRANTS

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