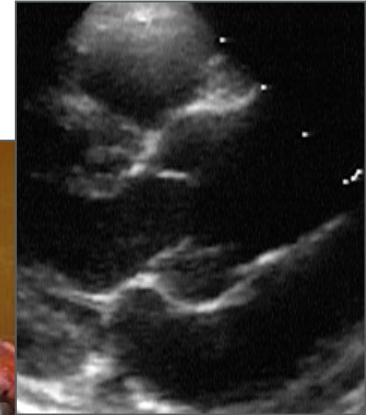
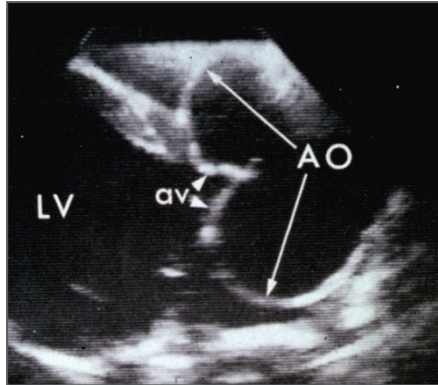




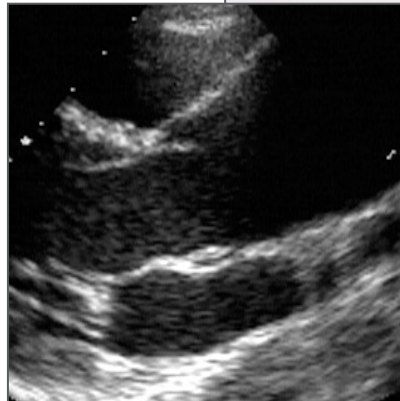
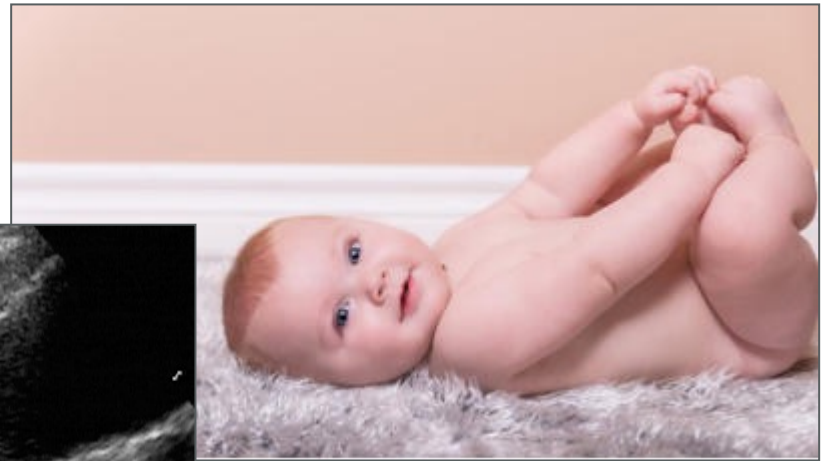
Perspectives in Pediatric Aortopathies: Vascular Genetics Symposium 2025

Kathryn W. Holmes, MD, MPH

Aortopathy/Arteriopathy and Connective tissue disorders in Children



<http://www.loeysdietz.org>



<http://bicuspidfoundation.com>





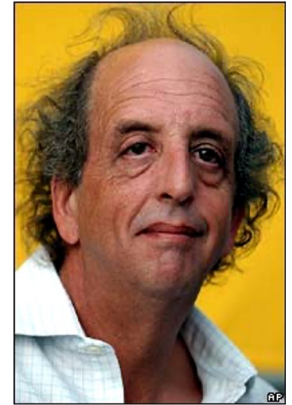
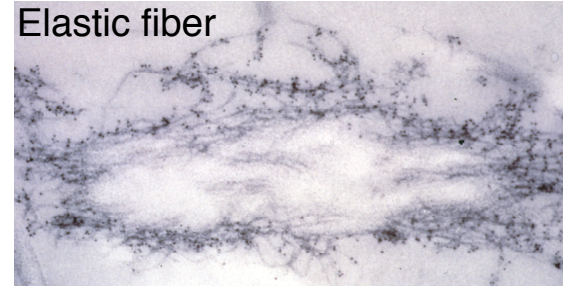
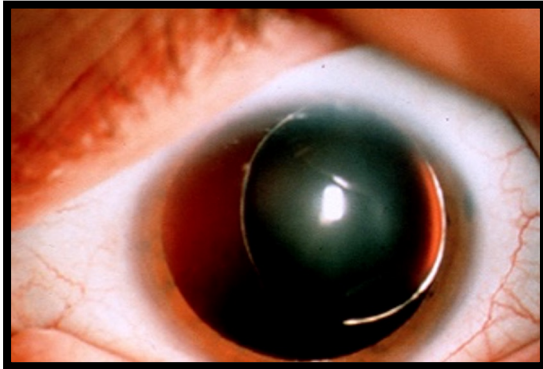
Talk Outline

- What are the syndromes in pediatrics and how do they impact childhood
 - HINT it is not all the heart/vasculature
- Genetics – skipping that
- Aortic size/Z scores/Medications
 - Skipping medications
- Exercise Considerations
- Lessons learned and notes on Emergencies

Genetic Syndromes with Aortic Pathology

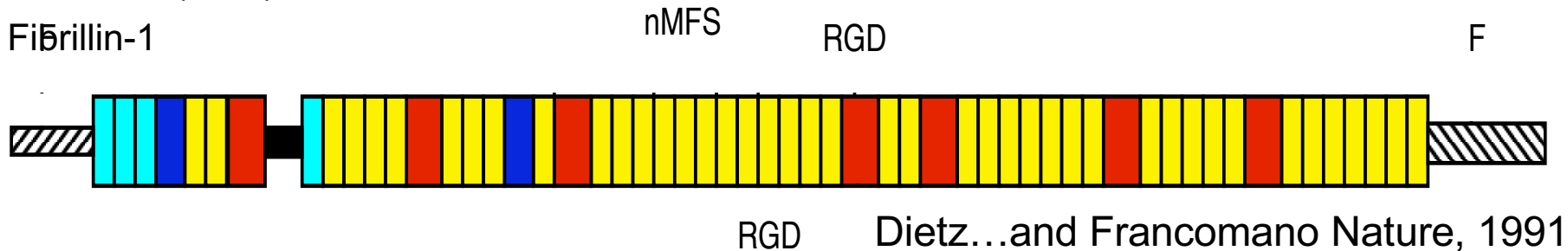
- Marfan Syndrome
- Ehlers-Danlos Syndrome, vascular type
- Loeys-Dietz Syndrome
- Turner syndrome
- Bicuspid aortic valve and aortopathy
- Shprintzen-Goldberg Syndrome
- BGN-associated aortic aneurysm syndrome
- MASS phenotype
- Arterial tortuosity syndrome
- Congenital contractual arachnodactyly
- Noonan syndrome
- Autosomal recessive cutis laxa
- Fibromuscular dysplasia
- Williams Syndrome

Marfan syndrome:

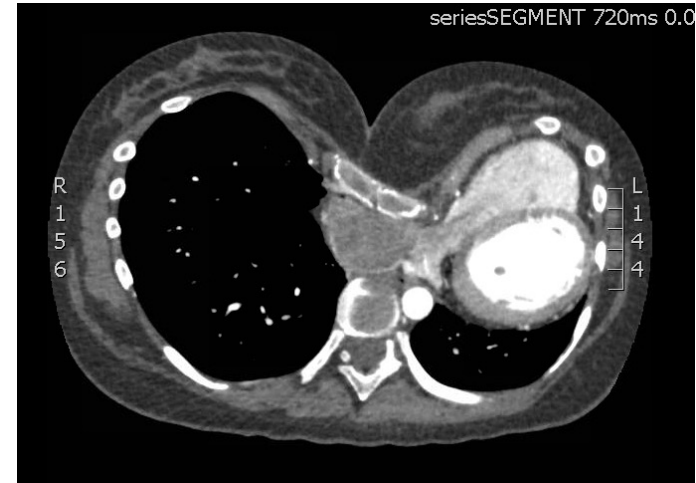
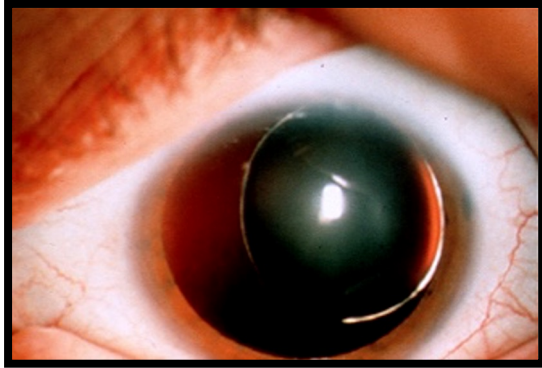


Fibrillin-1 (or -2)

FiBrillin-1



Marfan syndrome:



Associations of Age and Sex With Marfan Phenotype

The National Heart, Lung, and Blood Institute GenTAC (Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions) Registry

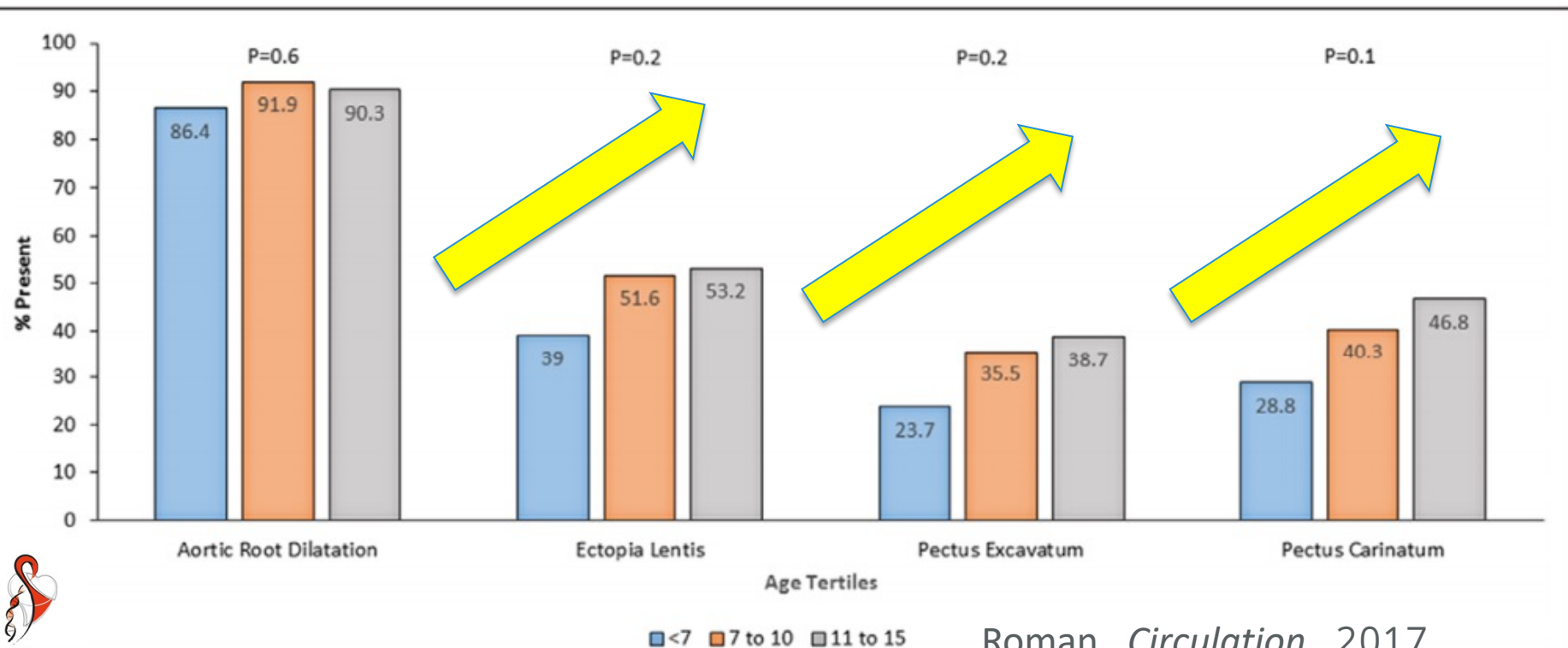
Mary J. Roman, MD; Richard B. Devereux, MD; Liliana R. Preiss, MS; Federico M. Asch, MD;
Kim A. Eagle, MD; Kathryn W. Holmes, MD, MPH; Scott A. LeMaire, MD;
Cheryl L. Maslen, PhD; Dianna M. Milewicz, MD, PhD; Shaine A. Morris, MD, MPH;
Siddharth K. Prakash, MD, PhD; Reed E. Pyeritz, MD, PhD; William J. Ravekes, MD;
Ralph V. Shohet, MD; Howard K. Song, MD, PhD; Jonathan W. Weinsaft, MD;
for the GenTAC Investigators*

- Increased prevalence by age in the following:
 - Arachnodactyly
 - Scoliosis
 - Skin Striae
 - Mitral valve prolapse

Associations of Age and Sex With Marfan Phenotype

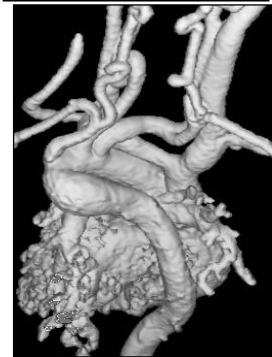
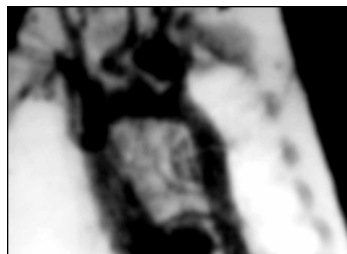
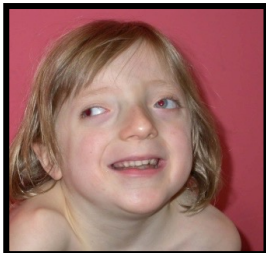
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for the GenTAC Investigators*



Roman, *Circulation*, 2017

Loeys-Dietz syndrome (LDS)



Like Marfan syndrome:

- curvature of spine
- chest wall deformity
- long fingers
- aortic root aneurysm

Unique:

- widely-spaced eyes
- cleft palate/bifid uvula
- premature skull fusion
- club foot deformity
- congenital heart disease
- arterial tortuosity
- diffuse aneurysms
- rupture / death young age
- PDA, BAV, ASD

(> 500 families)

Loeys et al., *Nature Genetics*, 2005

Loeys et al., *NEJM*, 2006

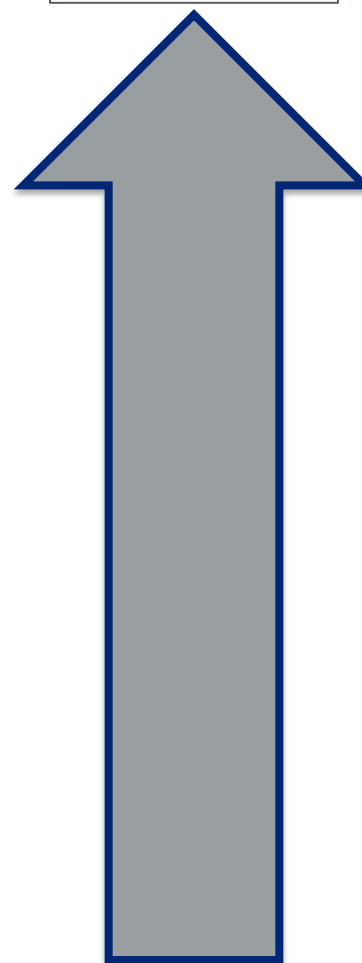
Gene	Nomenclature
TGFBR1	LDS, type 1
TGFBR2	LDS, type 2

Courtesy of Hal Dietz

Evolution of Loeys-Dietz:

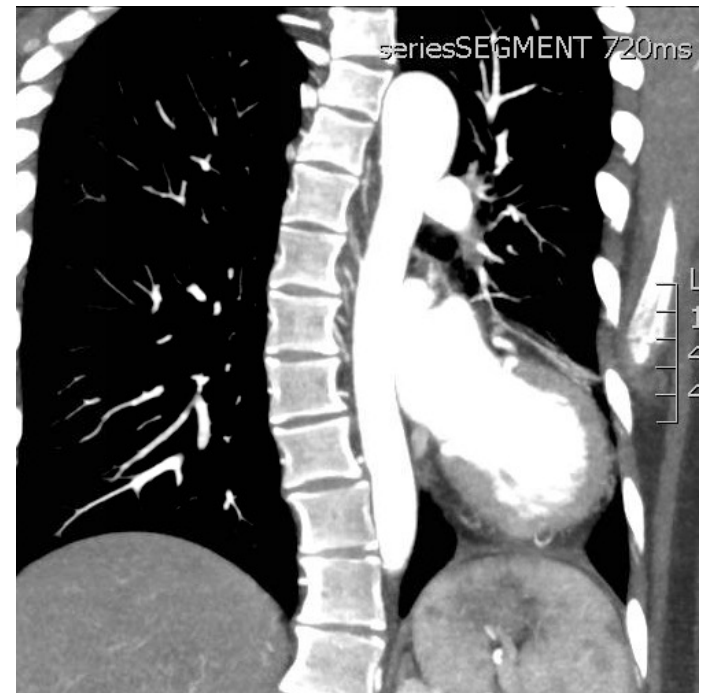
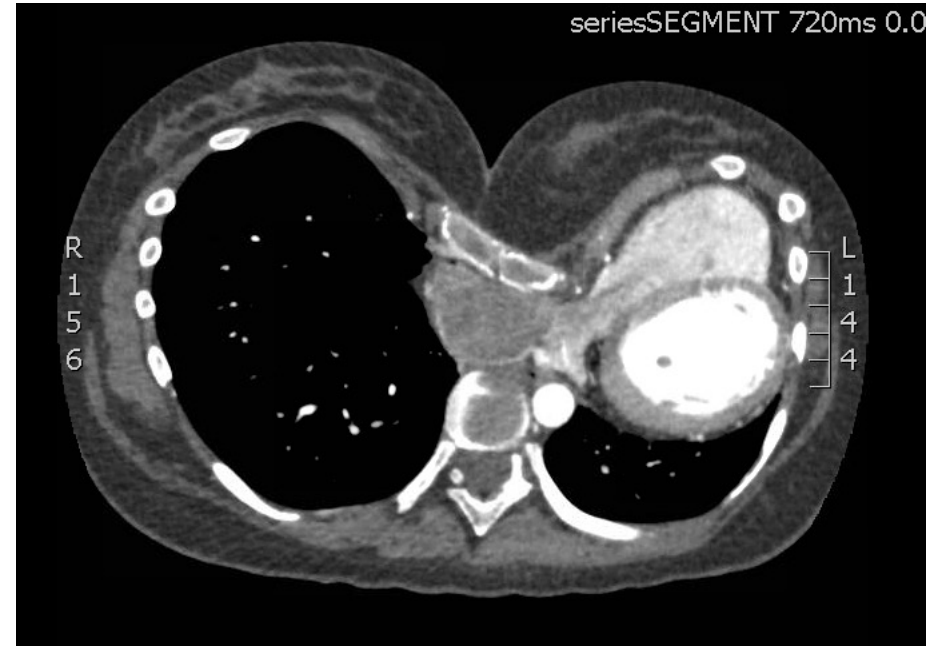
Gene	Nomenclature
TGFBR1	LDS, type 1
TGBR2	LDS, type 2
SMAD3	LDS, type 3
TGFB2	LDS, type 4
TGFB3	LDS, type 5
SMAD2	LDS, type 6
?	LDS, type 7

Phenotypic
Severity

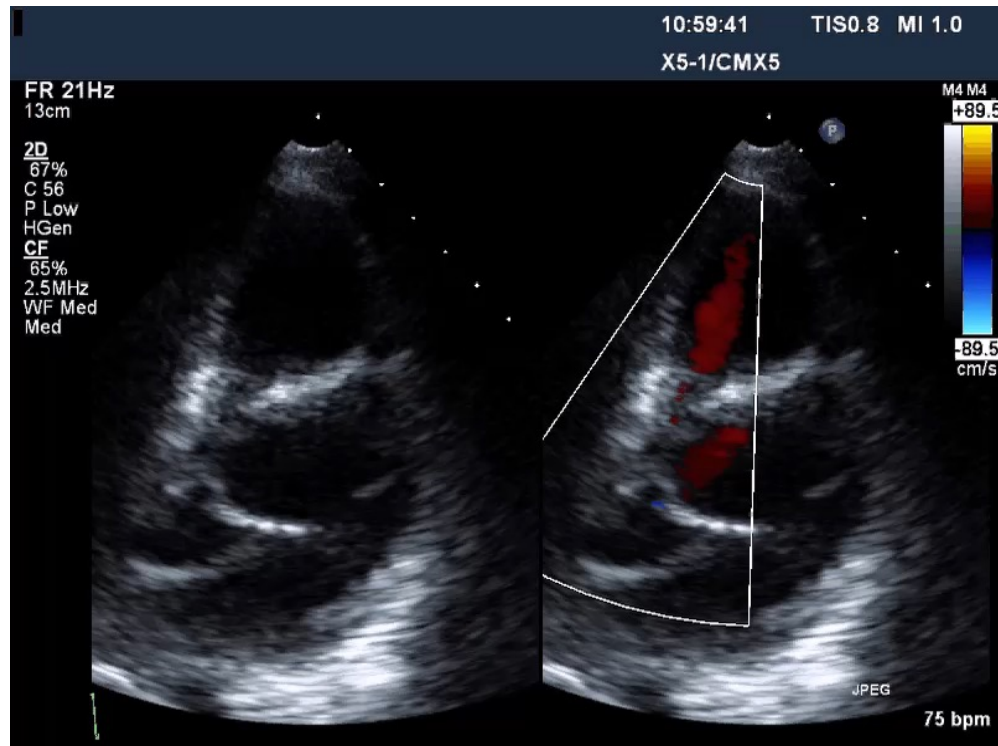


$TGF\beta R1$ example

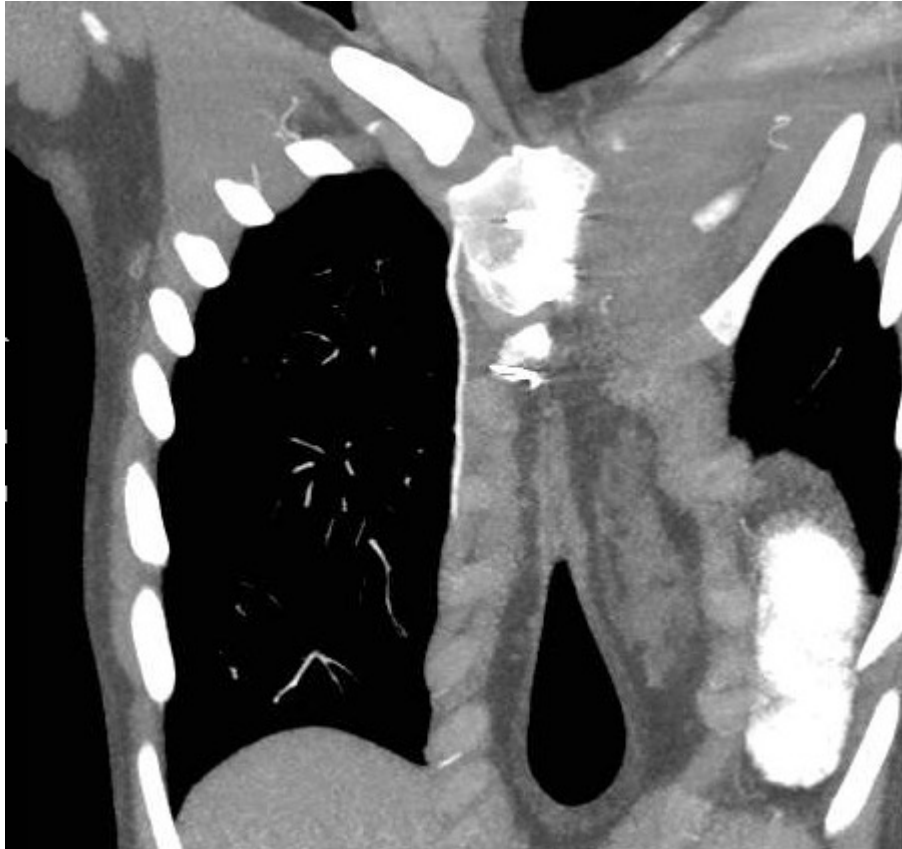
- Age 11
 - Aortic prophylactic aortic replacement, age 10
 - Mild Scoliosis
 - Severe pectus excavatum
 - Normal uvula
 - Absent right kidney
 - Bicornate uterus



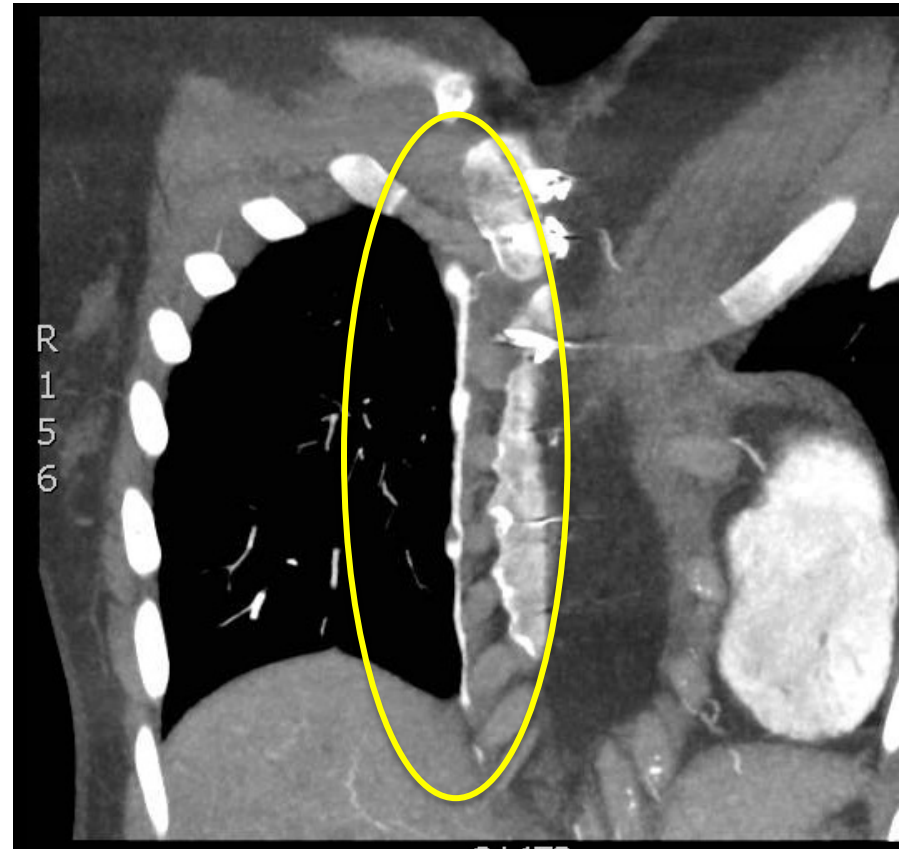
12 months after VSRR with $TGF\beta R1$



The Story Continues: *TGFBR1*



Age 14

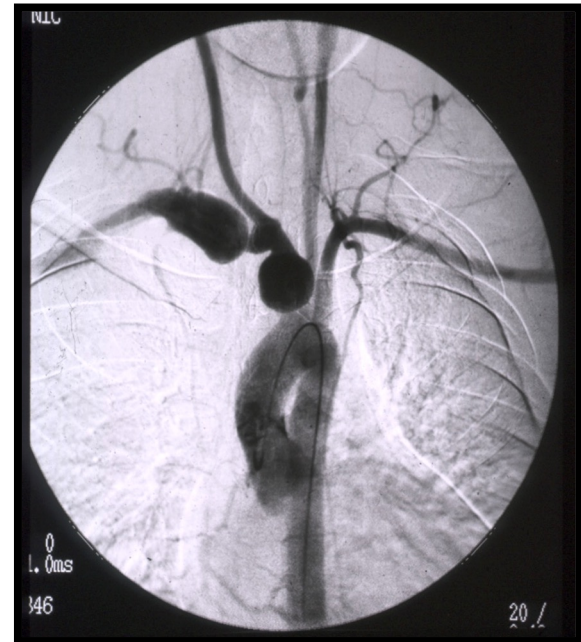


Age 16

Vascular Ehlers-Danlos Syndrome (vEDS)

Mutations in *COL3A1*
encoding type III collagen

- Aneurysm of any muscular artery
- Aortic root typically spared
- Dissection risk w/ or w/o prior dilatation
- High risk of operative complications
- Risk of hollow organ rupture (bowel or uterus)



Caitlin Bowen



vEDS: Pediatrics



Pneumothorax

Thin Skin

Varicose veins

Amniotic Bands

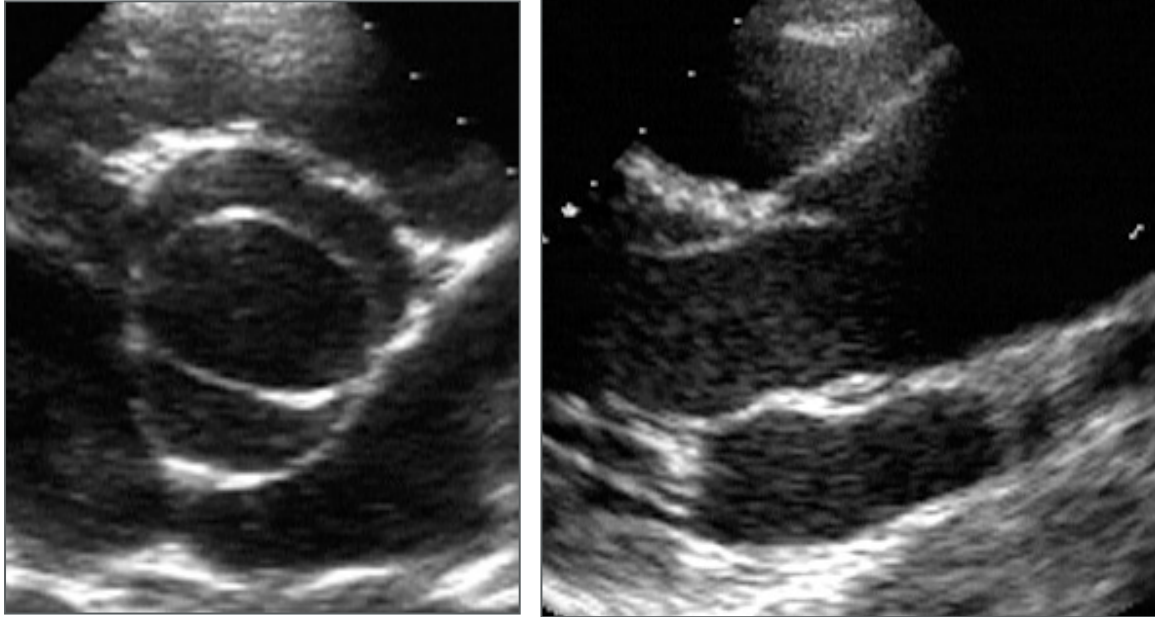
Joint hypermobility

Club Foot

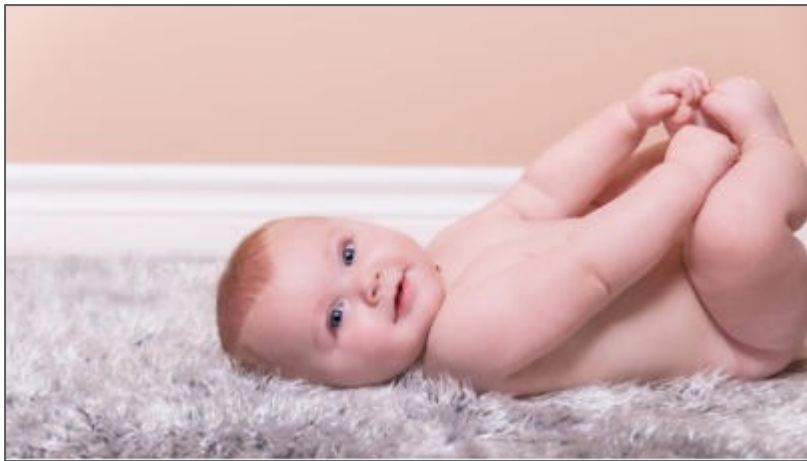
Aortic dissection/rupture

Lots of bruises

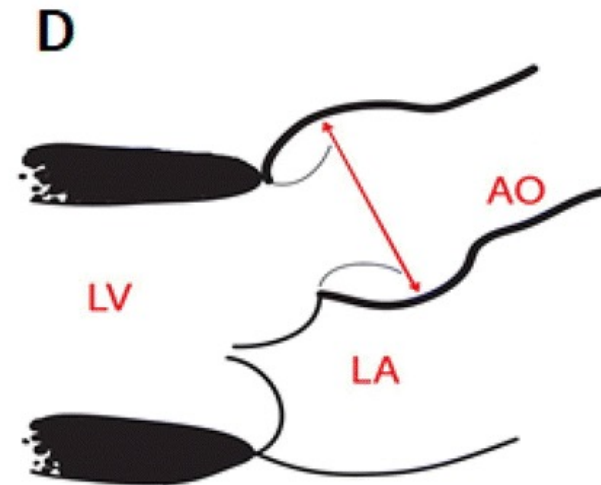
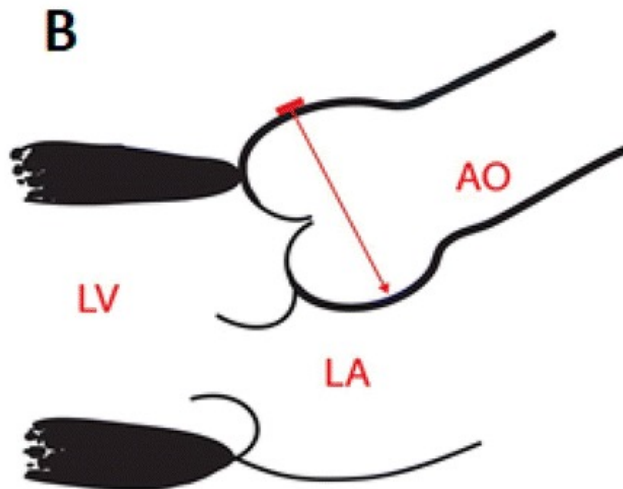
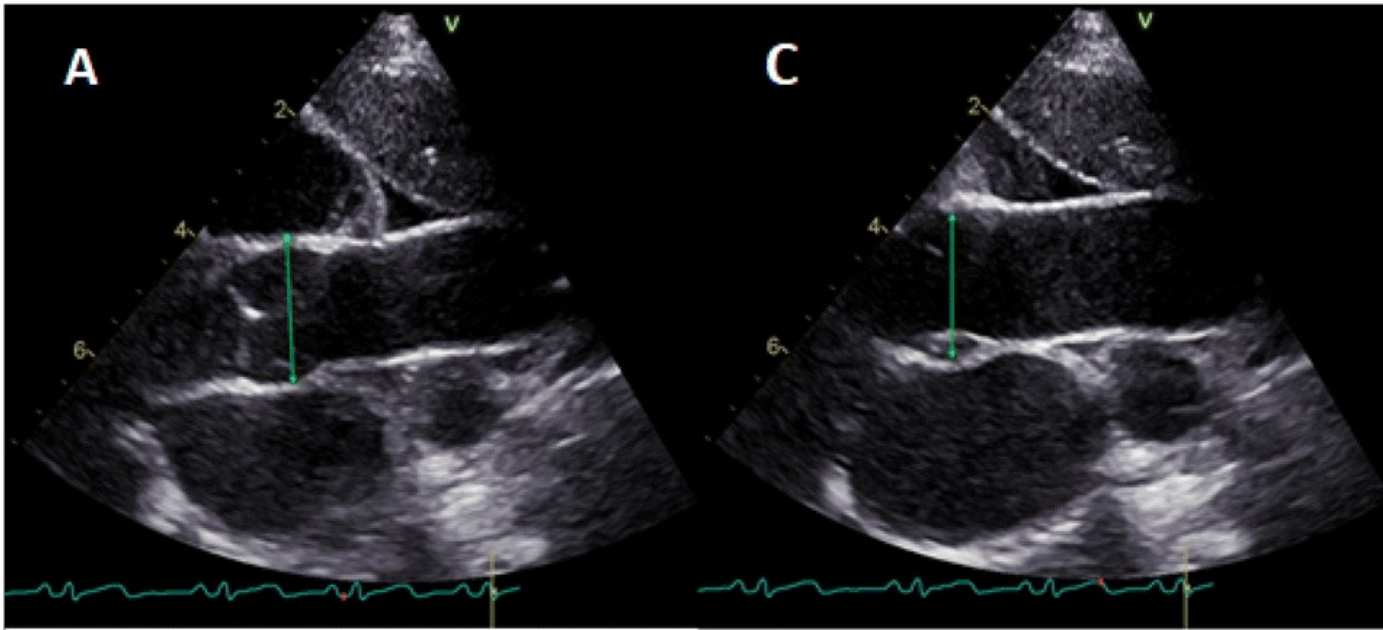
Bicuspid Aortic Valve



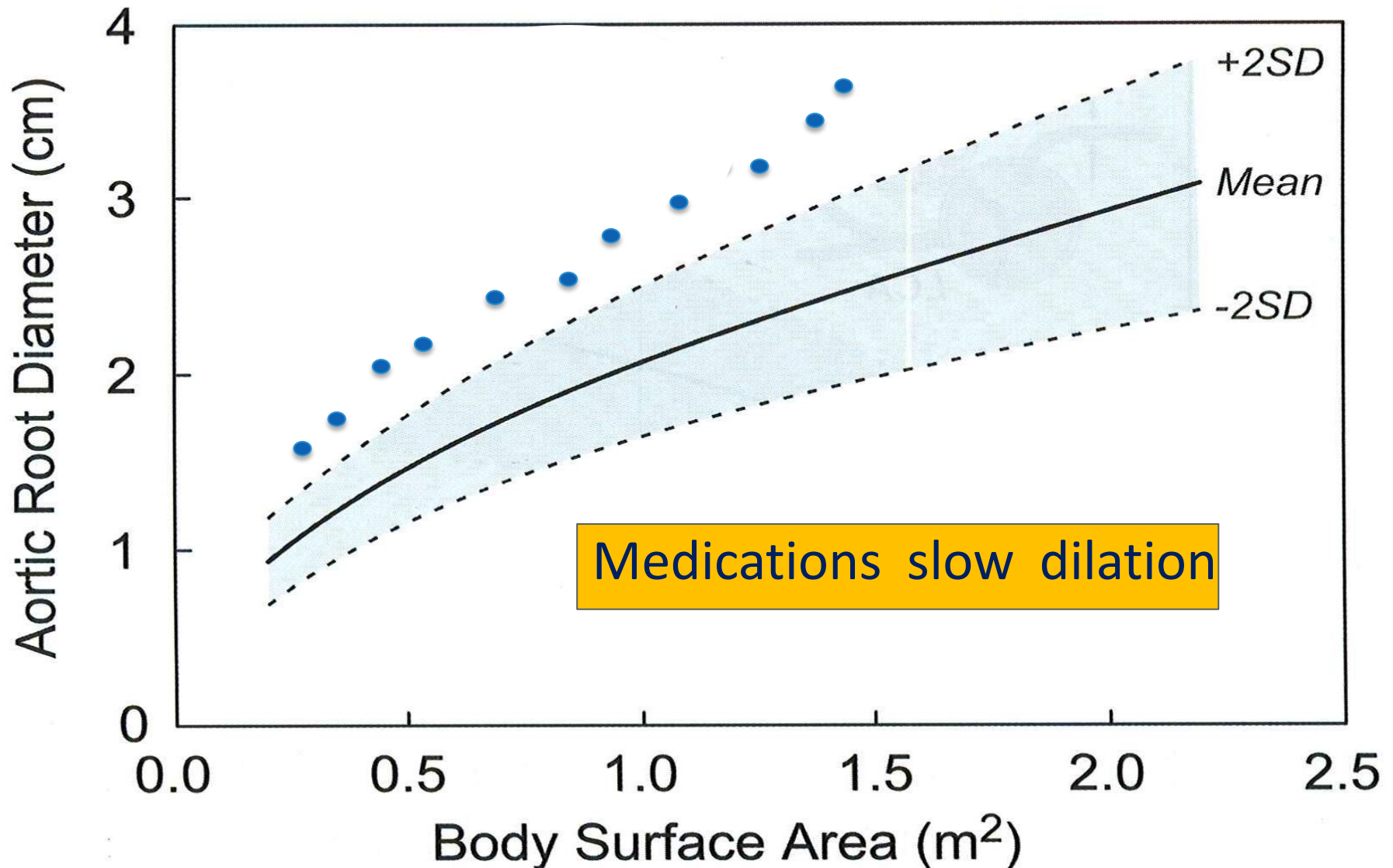
- Most isolated
- Can be associated with aortic stenosis, regurgitation, or aortic coarctation
- While some are associated with syndrome
- Autosomal dominant but poorly penetrant



Aortic measurement: Peds and Adult



Aortic Dilation: What is a Z score????



Medication strategy: Depends on the aortic size, mutation and family history

- Start with one medication – max out. Weight adjust over time
- On ARB – occasionally check renal function profile
- Add the second agent
- Serial imaging
- With normal aorta, shared decision making.



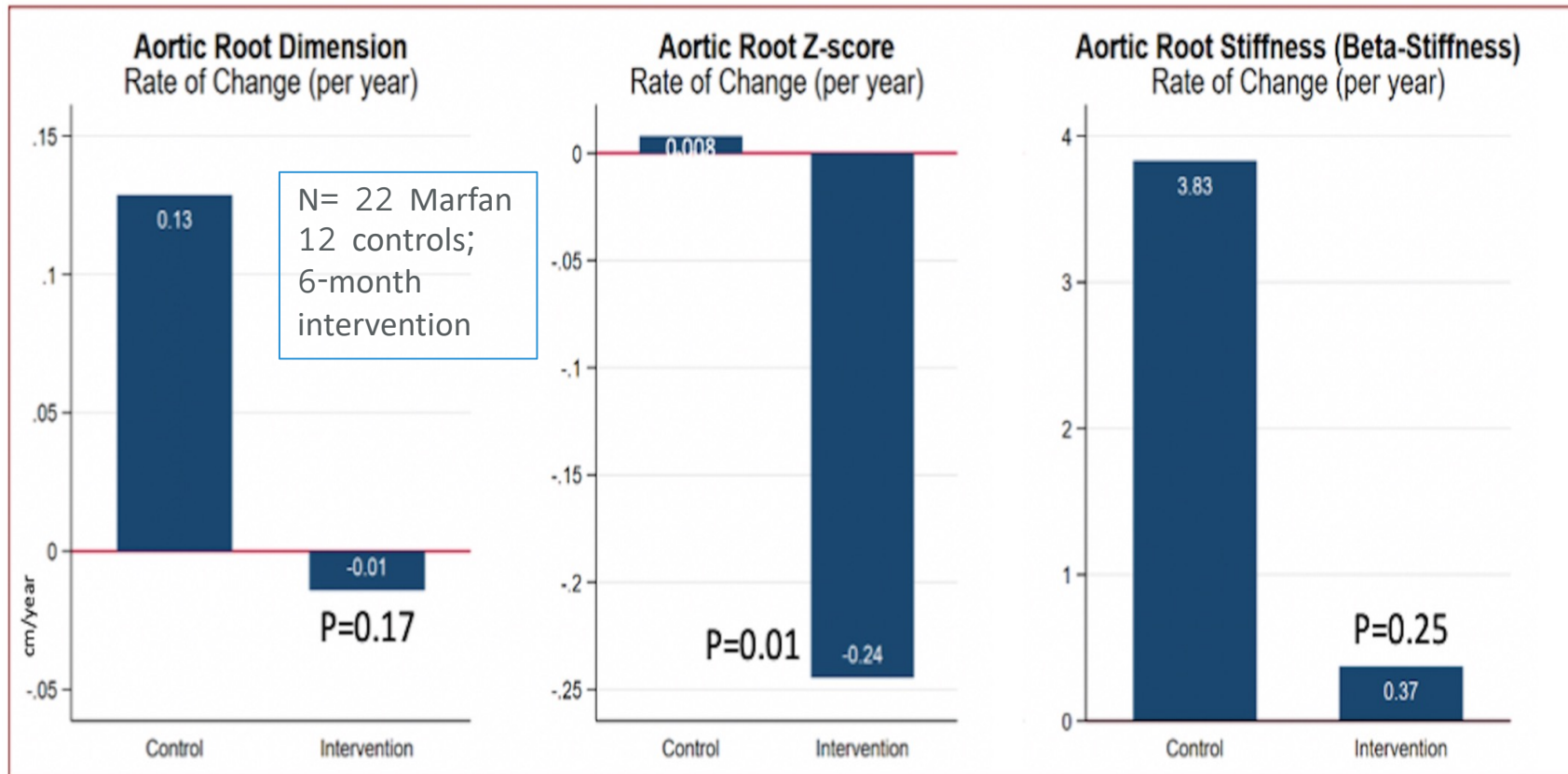


Exercise and sports: Kids

- Two world class athletes died of aortic dissection, prompting restrictions for sports participation in patients with aortopathies
- Pictured is Isaiah Austin, who was discovered to have Marfan during the NBA draft

Can 10 000 Healthy Steps a Day Slow Aortic Root Dilation in Pediatric Patients With Marfan Syndrome?

Elif Seda Selamet Tierney ^{ID}, MD; Sukyung Chung ^{ID}, PhD; Katie Jo Stauffer ^{ID}, RDCS;
Jerrid Brabender ^{ID}, RDCS; Ronnie Thomad Collins ^{ID} II, MD; Robert Folk ^{ID}, BSc; Weidang Li, PhD;
Ashlesh K. Murthy, MD, PhD; Daniel Jerome Murphy ^{ID}, MD; Mitra Esfandiarei ^{ID}, PhD

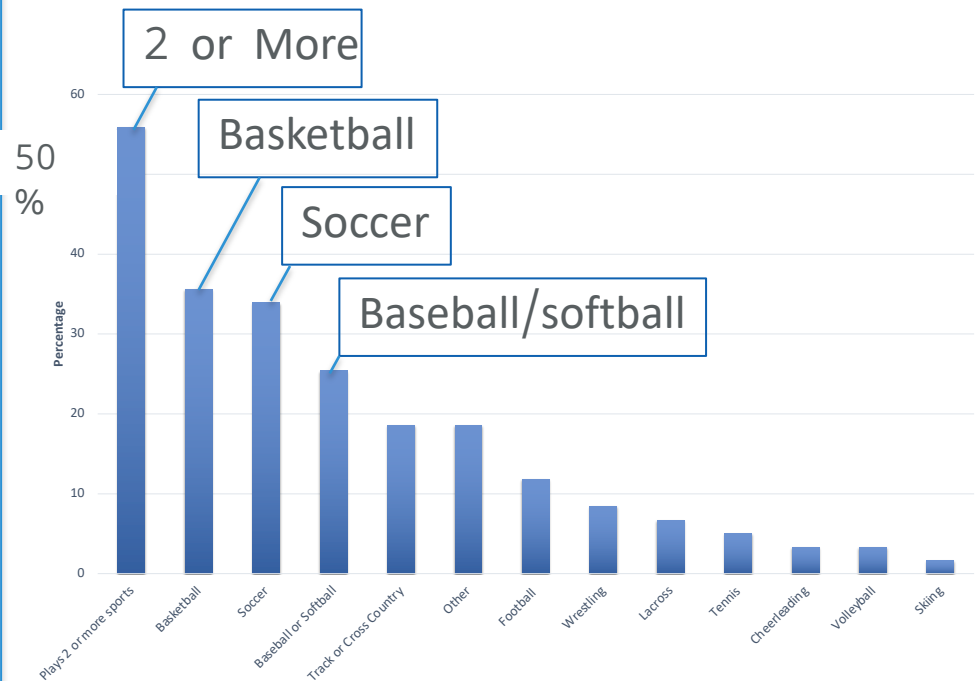


BAV and Exercise Survey

Table 3. Parent Survey Results

Question	Yes Results N=110 % (N)
Do you worry about your child because of their heart?	32 (35)
Does your child's cardiologist discuss activity?	79 (87)
Is it safe for your child to participate in moderate to vigorous physical activity?	96 (106)
Participate in more than 1 hour of moderate to vigorous physical activity?	36 (40)
Do you limit your child's physical activity?	9 (10)
Do you instruct your child's physical education teacher to limit their physical activity?	14 (15)
Does your child participate in competitive sports?	53 (58)
Has your child stopped a sport because their cardiologist recommended they do so?	7 (8)
Has your child asked to play a sport that you have not allowed them to due to concern about their heart?	22 (24)

Sports played by Athletes



Baleilevuka-Hart, Holmes, Huang, 2023

Impact of Regular Physical Activity on Aortic Diameter Progression in Paediatric Patients with Bicuspid Aortic Valve

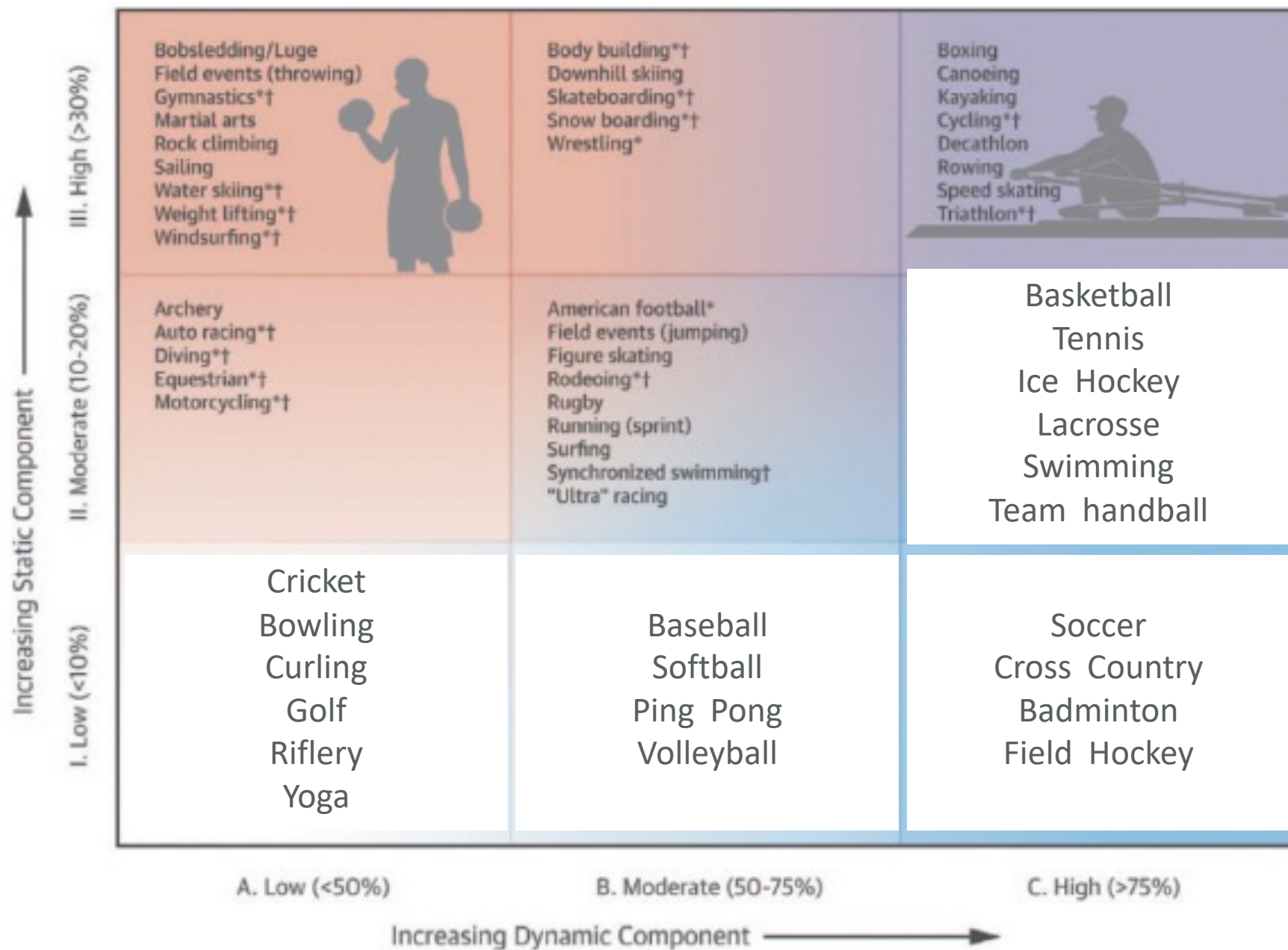
Emanuele Monda¹ · Adelaide Fusco¹ · Alessandro Della Corte¹ · Martina Caiazza¹ · Annapaola Cirillo¹ · Felice Gragnano^{1,2} · Maria Pina Giugliano¹ · Rodolfo Citro³ · Marta Rubino¹ · Augusto Esposito¹ · Arturo Cesaro^{1,2} · Francesco Di Fraia¹ · Giuseppe Palmiero⁴ · Marco Di Maio¹ · Marcellino Monda⁵ · Paolo Calabrò^{1,2} · Giulia Frisso⁶ · Stefano Nistri⁷ · Bicuspid Aortic Valve Consortium (BAVCon) · Eduardo Bossone⁸ · Simon C. Body⁹ · Maria Giovanna Russo¹ · Giuseppe Limongelli^{1,10} 

- Prospective Observational Design, 2-year follow-up
- 90 patients, 53-active, 37-sedentary
- Definition of physical activity: “practiced regular leisure-time physical activity at least three times a week for at least 10 months a year for the entire follow-up period.”
- Mean age at enrollment 13.2 ± 2.5 , 9.3 ± 3.0 ($p < 0.001$)
- No difference in absolute or Z score change in ascending or aortic root

Activity Recommendations: Children

- Do move as much as you can
- It is okay to play recreational sports in elementary and middle school
- Continuing high competitive sports depend on your risk profile but stopping sports if that is your social circle can be challenging
- We extrapolate weightlifting from other data
- Use the guidelines.

FIGURE Classification of Sports



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 Quintero, MD; Elizabeth S. Cappella, APRN-NP; Harry C. Dietz, MD; Dianna M. Milewicz, MD, PhD; Maral O. Ozyurt, MD; Christina M. Rigelsky, MS, CGC; Seda Tierney, MD, FAHA; Ronald V. Lacro, MD, Chair; on behalf of the American Heart Association Council on Lifelong Congenital Heart Disease and Heart Health in the Young (Yong-Ming Dai, MD, FAHA, Chair); Council on Cardiovascular and Stroke Nursing; Council on Peripheral Vascular Disease; Council on Cardiac Surgery; Council on Perioperative and Resuscitation; and Council on Cardiovascular Surgery and Anesthesia

Shared decision making

Table 4. Exercise and Activity Considerations by Age, Diagnosis, and Intensity

Consideration	Age 0–5 y (preschool)	Age 5–10 y (elementary school)	Age 10–14 y (middle school)	Age 14–18 y (high school)
Counseling				
	Introduce main concept of shared decision-making Provide guidance and reassurance for exercise safety and organized athletics (moderate intensity); with routine supervision, general play is safe and strongly encouraged	Revisit shared decision-making process: discuss lifelong cardiovascular health habits Help identify and encourage specific activities and team positions that decrease risk of exertion, collision, and repeated intense training Explore safe outdoor recreational habits (eg, buddy systems) Counsel regarding pediatric hypertension and obesity		Solidify shared decision-making process: identify and support lifelong cardiovascular health, help balance risks and benefits of desired activities, advise against high-risk adolescent behaviors (eg, substance abuse, smoking, vaping) and sedentary habits
Exercise and activity prescription				
Routine physical activity	Encourage regular childhood play (minimum 1–3 h/d)	Encourage regular moderate cardiovascular physical activity (30–60 min/d, 5 d/wk) as a healthy lifestyle choice		
Physical education	Encourage complete participation		Encourage routine participation; peak exertion activities discouraged (eg, rope climbing, timed sprints, push-up/pull-up competitions)	
Recreational sports	Encourage complete participation		Encourage routine participation with avoidance of contact sports (eg, tackle football, hockey, wrestling)	
Competitive sports		Competitive sports may be considered with regular risk/benefit discussions; avoid contact sports (eg, tackle football, hockey, wrestling) and high-intensity training, leagues, and competitions		
Amusement parks	Encourage full participation per size limitations	Caution may be warranted for high-intensity rides, including those with abrupt stops and starts in high-risk groups; use all proper safety equipment		
Intensity				
	Encourage developmentally appropriate childhood play	Encourage all age-appropriate recreational sports and group activities, including physical education class; frequent mild to moderate cardiovascular activity is safe and healthy		
			Guidance toward organized sports, certain team positions, and recreational activities with lower risk for bodily collision, physical trauma, strenuous training, or frequent unsupervised exertion Avoid strenuous training and prolonged physical exertion, heavy weightlifting (requiring forceful Valsalva), and sustained exertion to exhaustion	
				Encourage lower-intensity varsity and junior varsity athletics, club sports participation Refrain from more intense training or competition for highly select state or regional travel teams, Olympic development programs, collegiate varsity recruitment
Higher-risk criteria: diagnosis-specific considerations				
Marfan syndrome Lens subluxation Retinal detachment Joint hypermobility	Loeys-Dietz syndrome Joint hypermobility Atlantoaxial instability	Vascular Ehlers-Danlos syndrome Internal organ and arterial perforation with minimal trauma Prone to dislocations Avoid trampolines in addition to guidelines	FLNA deficiency Extreme joint hypermobility	Bicuspid aortic valve Moderate to severe valvular disease

	Low risk
	Low risk with modification as indicated
	Higher risk

Exercise by Age Group



Shared decision Making



Courtesy of OHSU

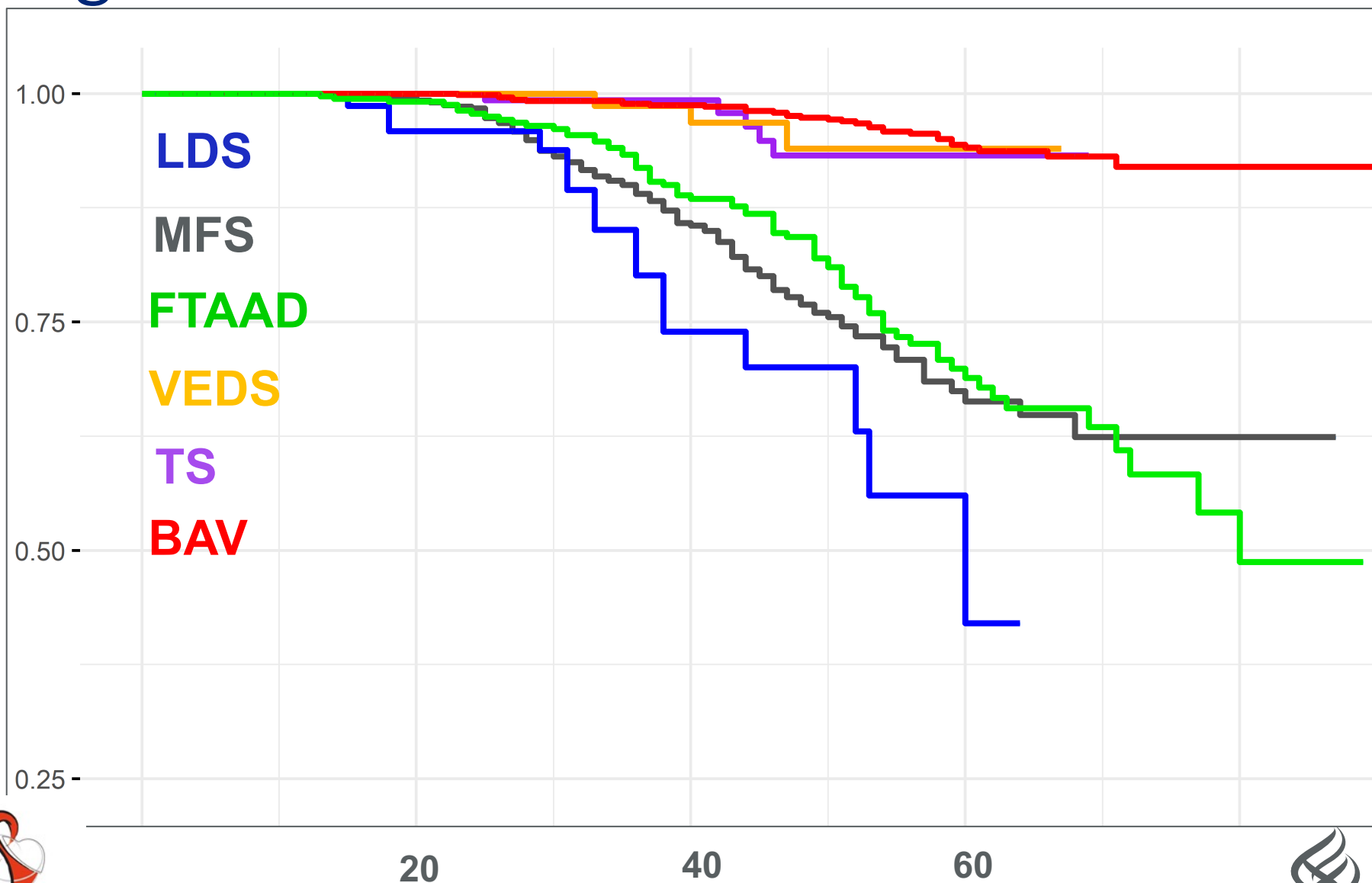
Age 10-13	Age 14-18 (and beyond)
Guidance toward organized sports, certain team positions, and recreational activities with lower risk for bodily collision, physical trauma, strenuous training, or frequent unsupervised exertion	
Avoid strenuous training and prolonged physical exertion, heavy weightlifting (requiring forceful Valsalva), and sustained exertion to exhaustion	
	Encourage lower-intensity varsity and junior varsity athletics, club sports participation
	Refrain from more intense training or competition for highly select state or regional travel teams, Olympic development programs, collegiate varsity recruitment



Emergencies: Single physician experience:

- Marfan
 - 0 deaths, 0 dissection
 - 2 pneumothorax
 - 1 MV chordal rupture
- TGFB
 - 1 aortic dissection – survival
 - 1 subclavian dissection - death
- vEDS
 - Aortic 1 dissection/rupture – death
- Many many CT scans, evaluations

Age at Dissection: GenTAC Data



International Registry for Aortic Dissection (IRAD): 20 years

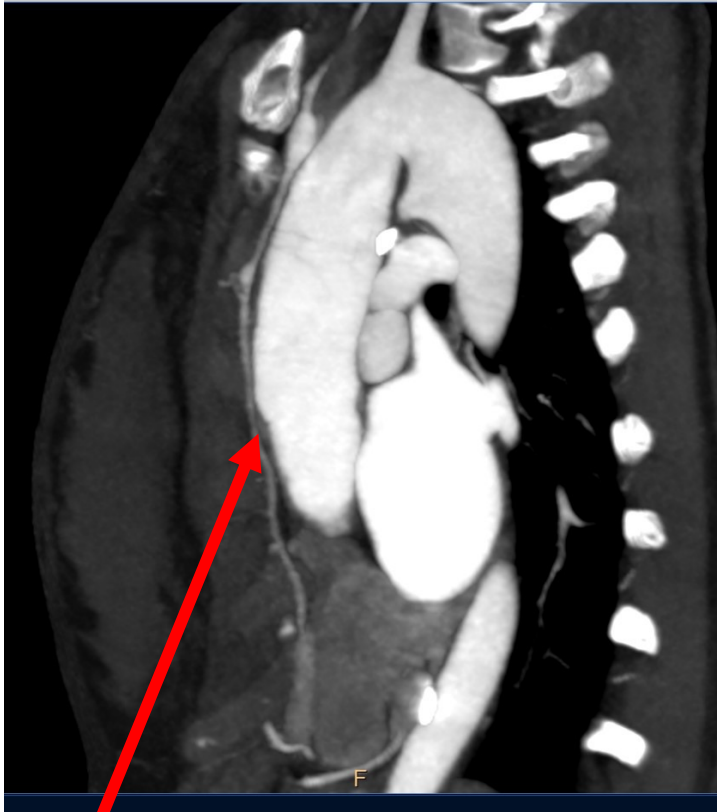
Dissection was more rapidly diagnosed when CT tomography or echocardiography

- MRI or an aortogram were performed, the diagnosis was delayed, often significantly

Delays in AAD diagnosis occurred more often in

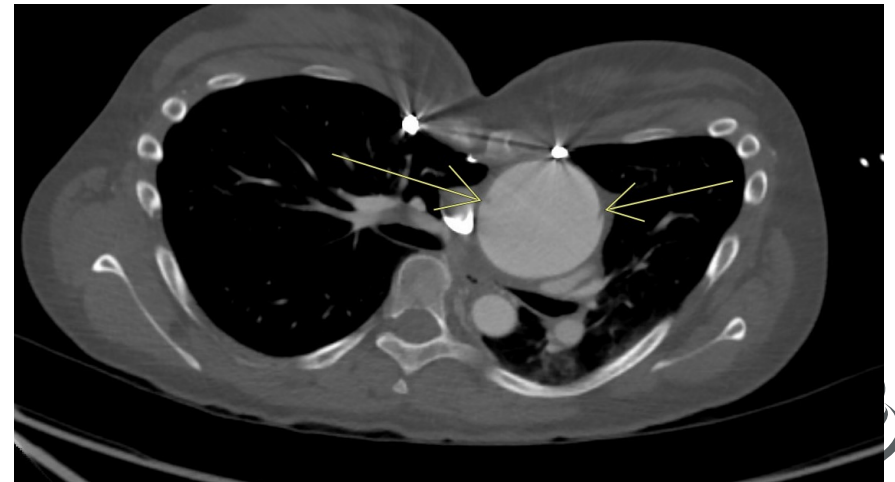
- female patients
- those with atypical symptoms that were not sudden or did not include pain
- those with previous cardiac surgery
- those who initially attended a non-tertiary care hospital (all $P < 0.05$).

Back to the $TGF\beta R1$ example



VSRR
superior
anastomosis

- Symptoms began at ~1900
- Severe sudden onset left sided chest pain 8/10
- Shortness of breath
- Worse with coughing
- No syncope or near syncope
- She presented to an outside ED about 45 min after onset.
- On presentation she was alert and oriented
- Pain and SOB had become intermittent



Emergency Preparedness: What I tell my patients

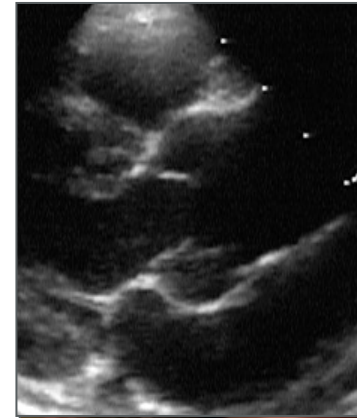
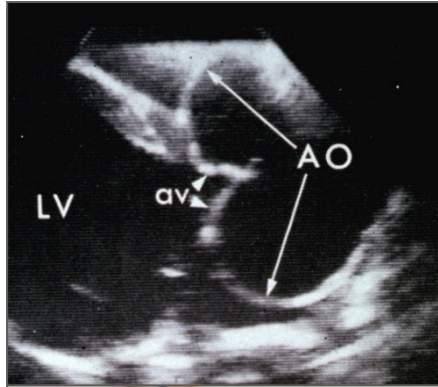
- Get a bracelet or have a card in your wallet
- If you experience a sudden onset of chest pain, back, pain, abdominal pain or head ache that is unusual and does not resolve, go to the ED
- If you have sudden onset of shortness of breath that does not resolve, go to the ED
- If you go to the ED, call us
- Tell the ED you have XX and are at risk of dissection.



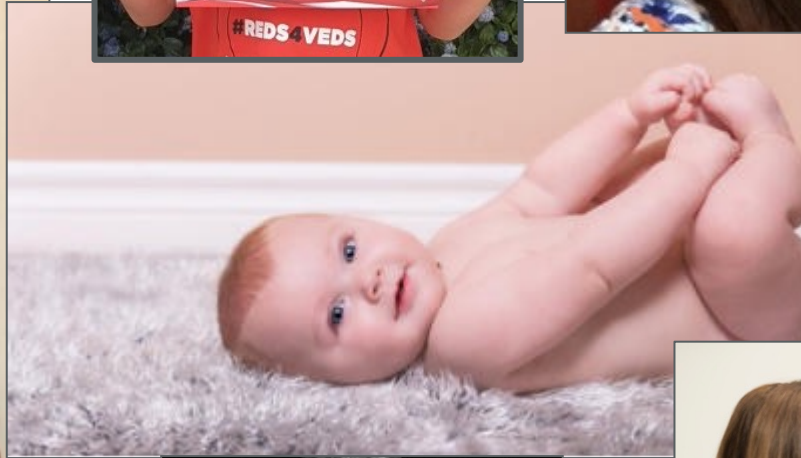
Take Home Pearls: Pediatrics

- Genetics -> Cascade screening.
- Management -> it's not just the heart
- Medications -> Slow the process
- Exercise-> It's okay to play
 - Shared decision making
- Aortic dissection -> rare in childhood but not unheard of
- Emergencies -> Have an action plan.
Expect the unexpected

Thank you



<http://www.loeysdietz.org>



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