Marfan Syndrome and other Ascending Aortic Aneurysmal Disease

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Torino, Italy

September 2013

No disclosures
Off label use of Losartan

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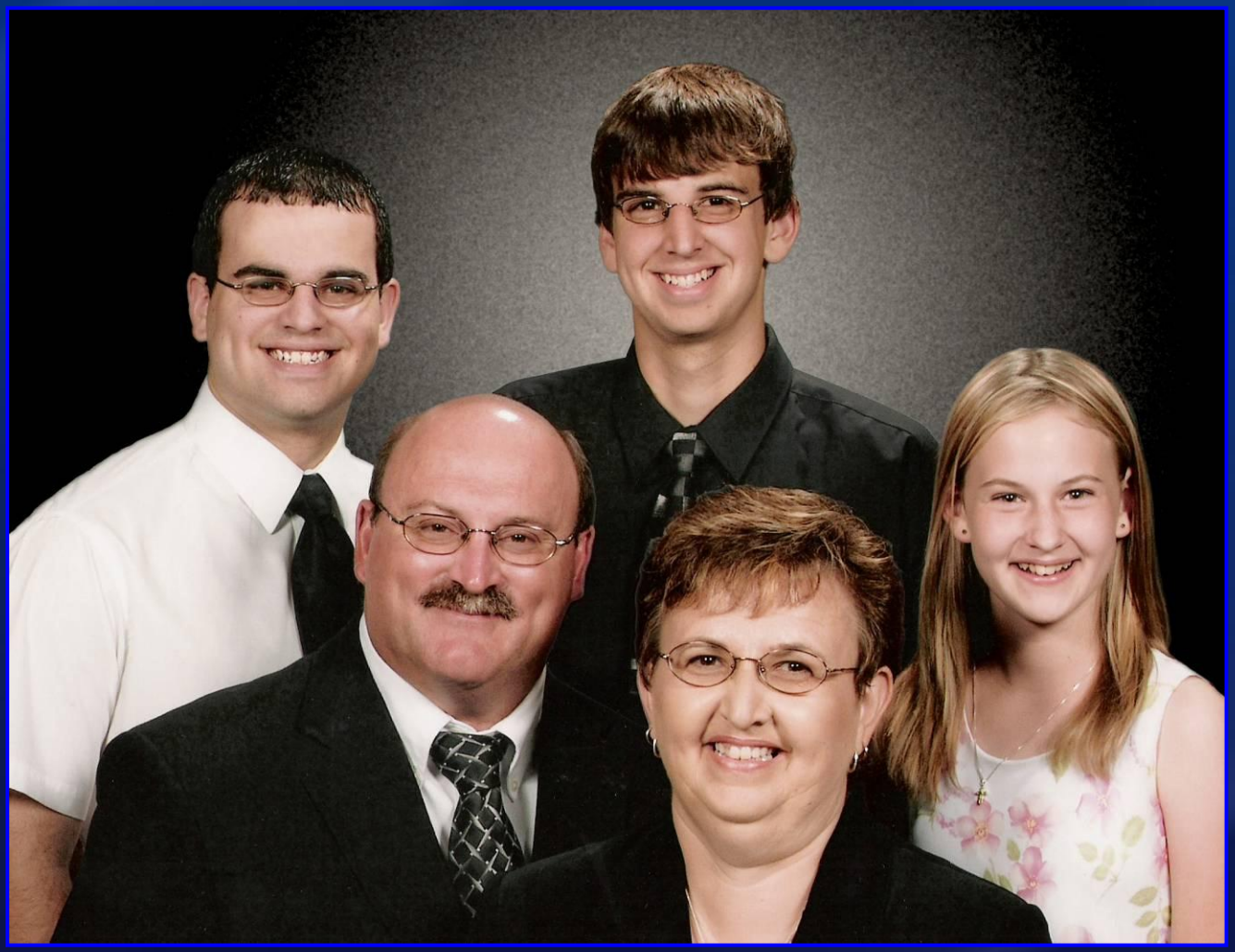

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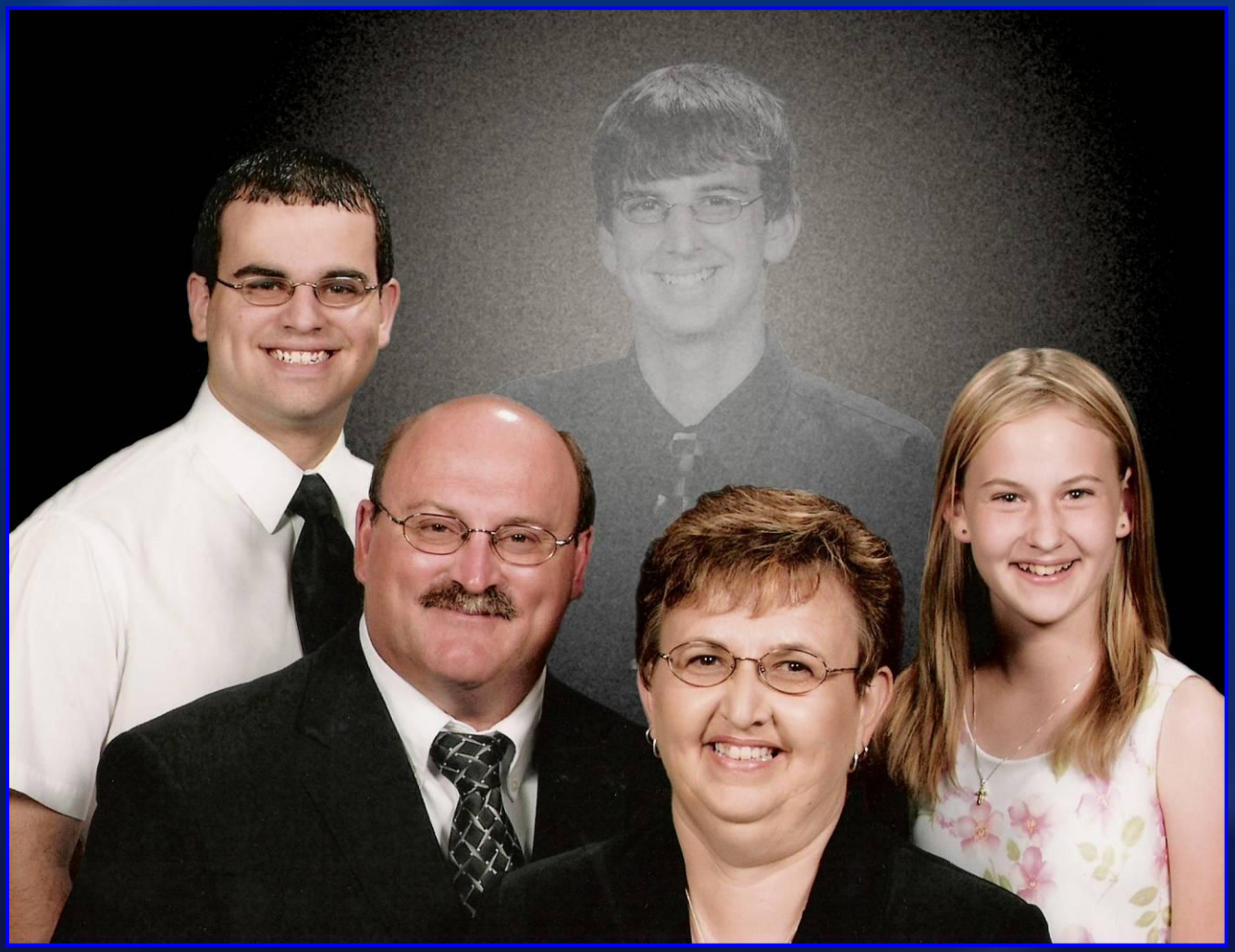

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48-Year-Old Female

- Presents for family screening

  18 yo son – died of aortic dissection

- No symptoms

- No prior suspicion of Marfan syndrome (MFS)

  Scoliosis surgery, pectus, flat footed

  Pectus excavatum

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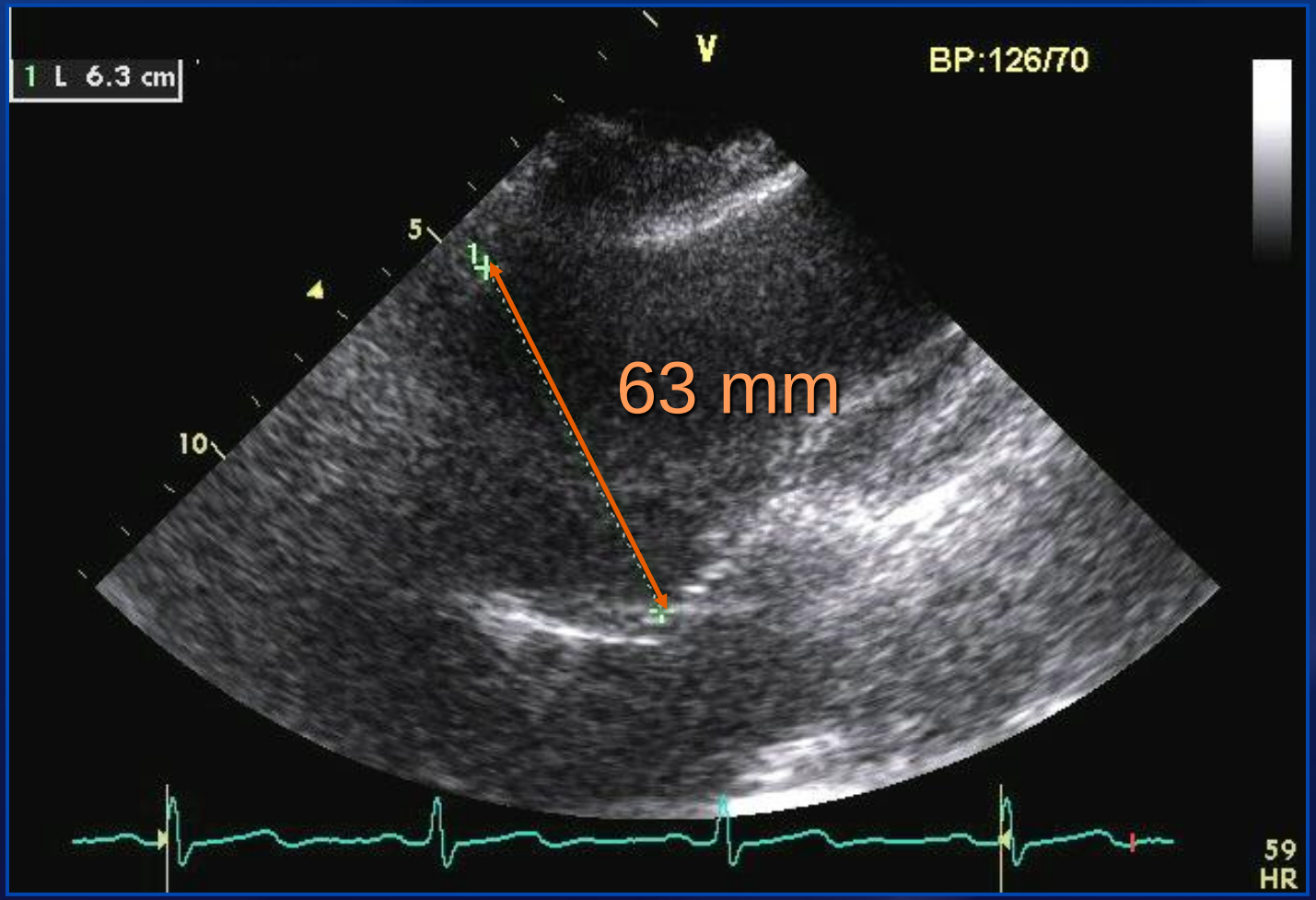
48-yr-old Female

Family History of Aortic Dissection



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What would you recommend?

Operation now

CT or MRI of the aorta

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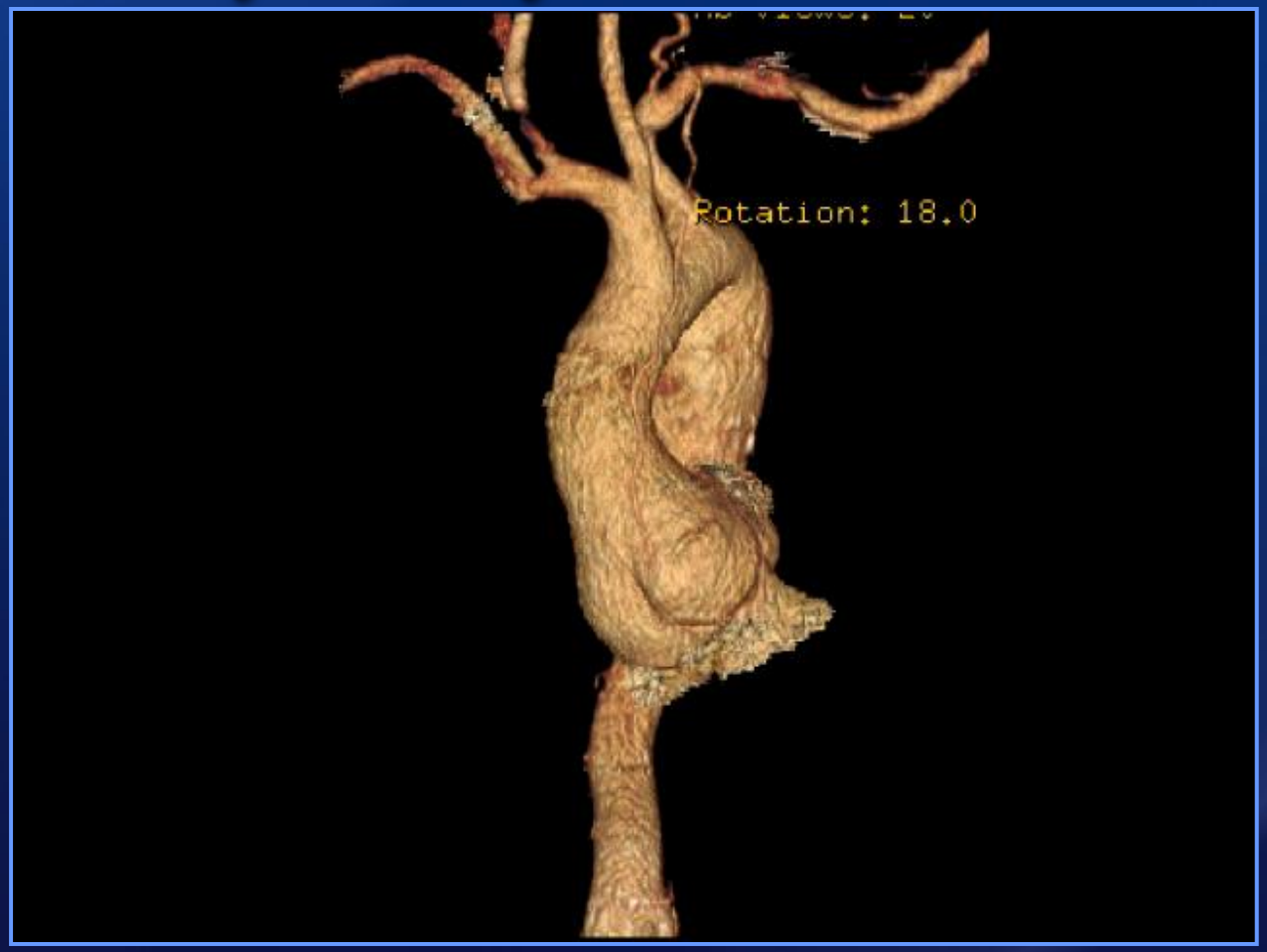
48-yr-old Female

Family History of Aortic Dissection



Confirmed asc aorta dimension obtained by TTE

Another aneurysm detected

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Patient Follow-up

- Urgent composite root replacement
- Genetics - *FBN1* positive
- Subsequent descending aorta replacement

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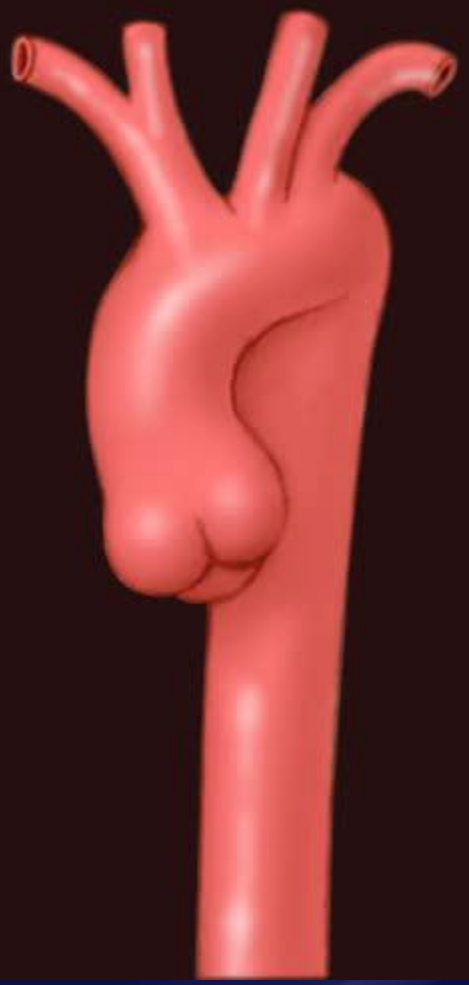
Aortic Media



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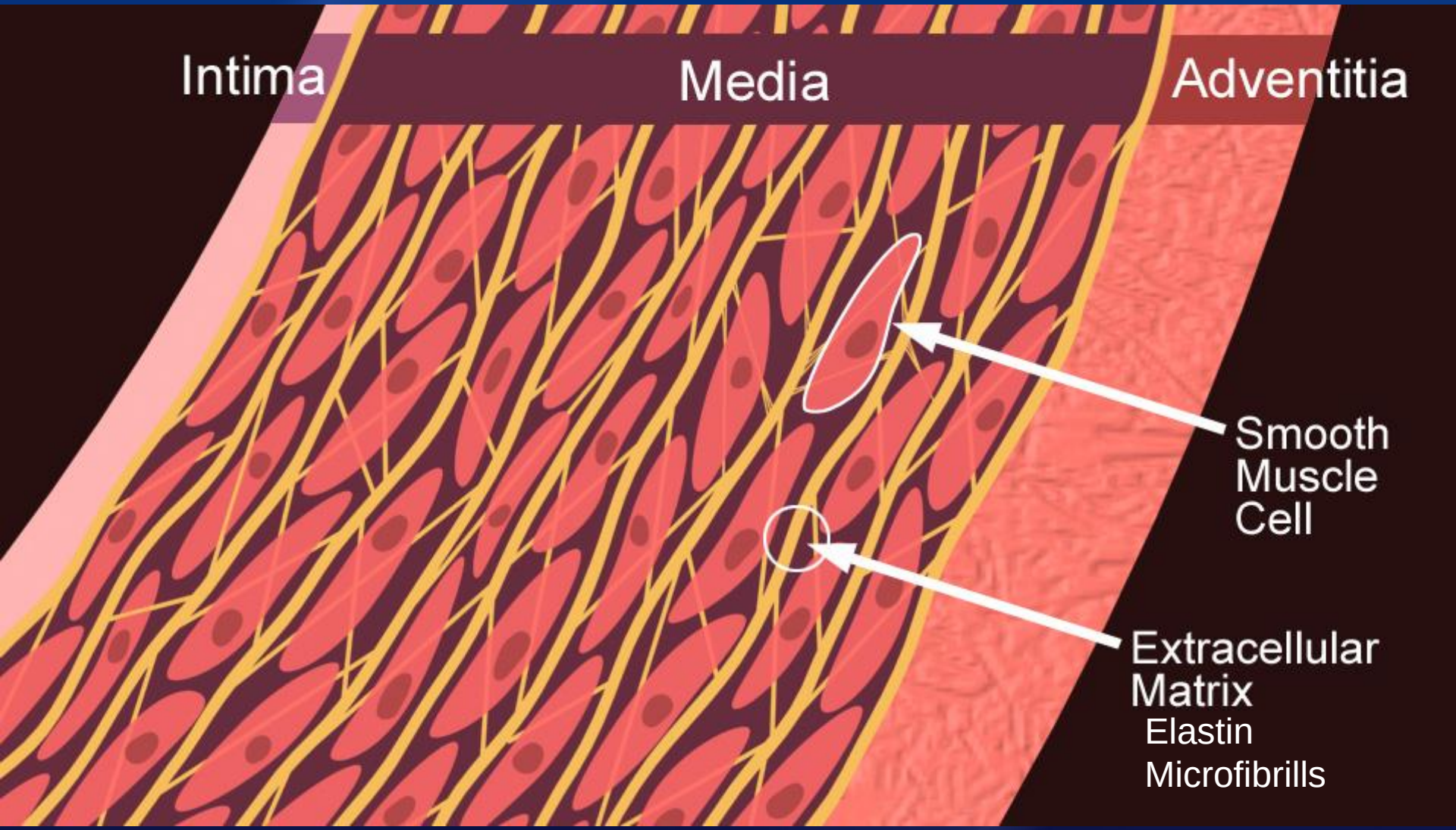

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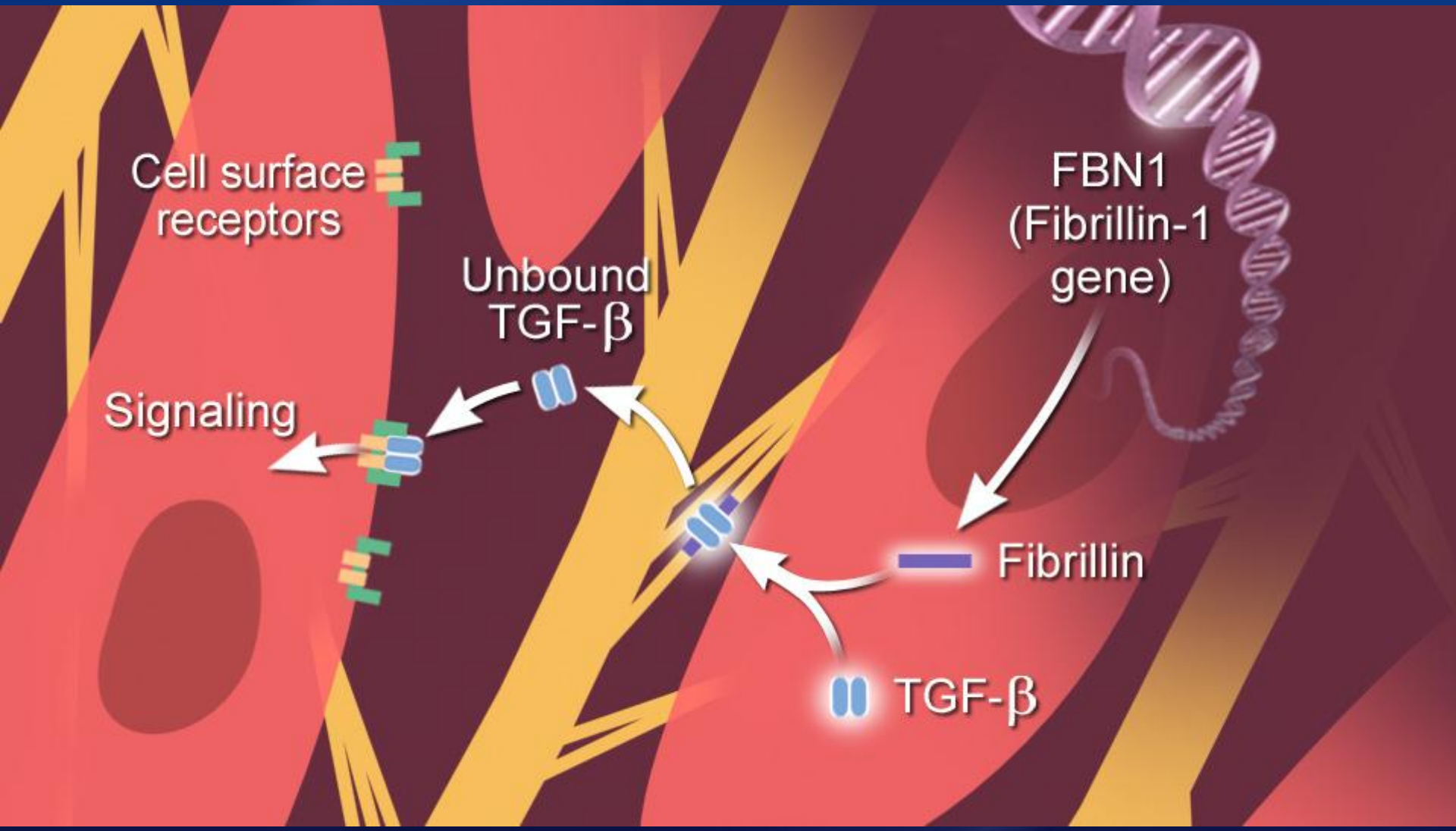

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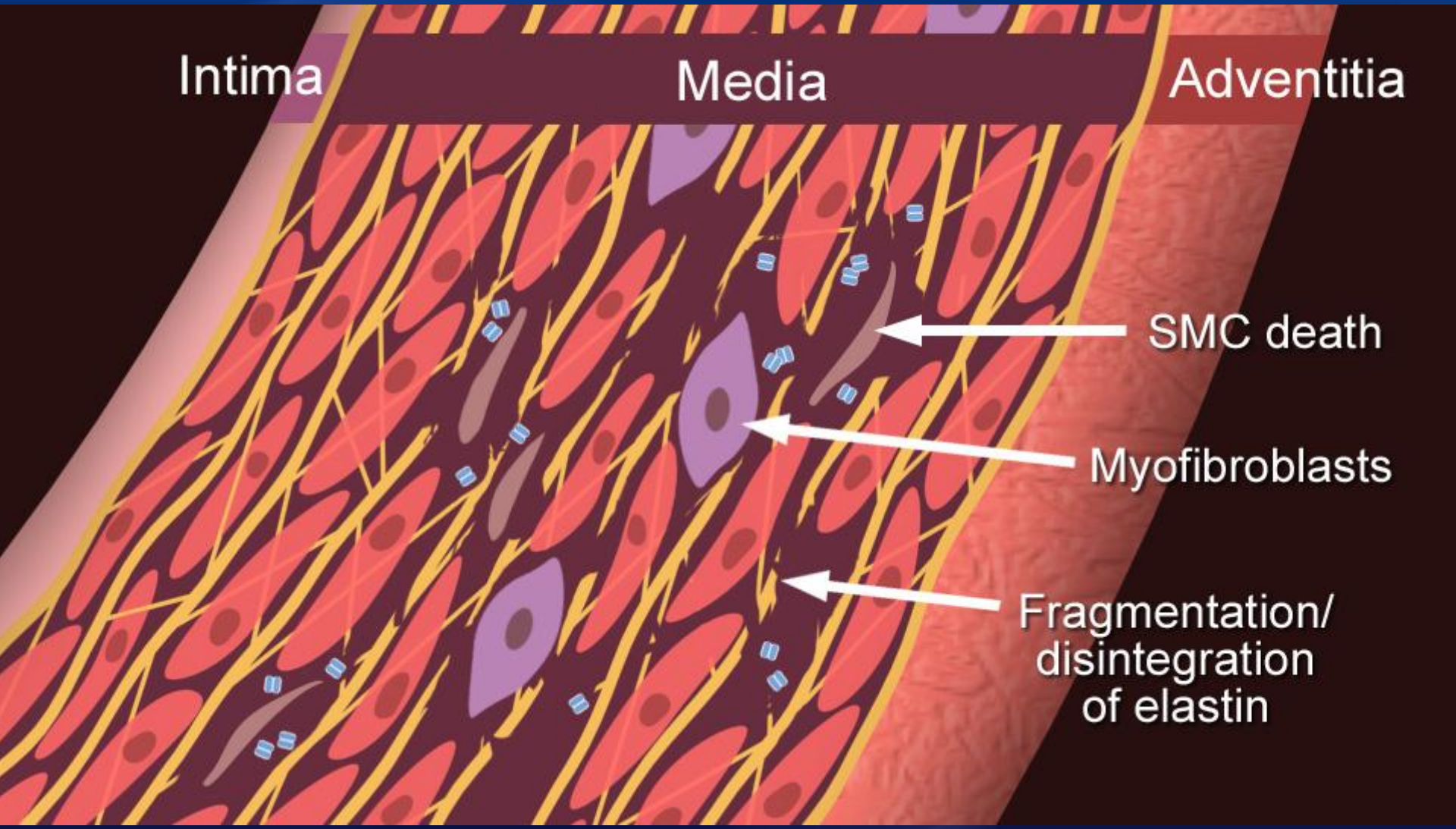
Medial Disease



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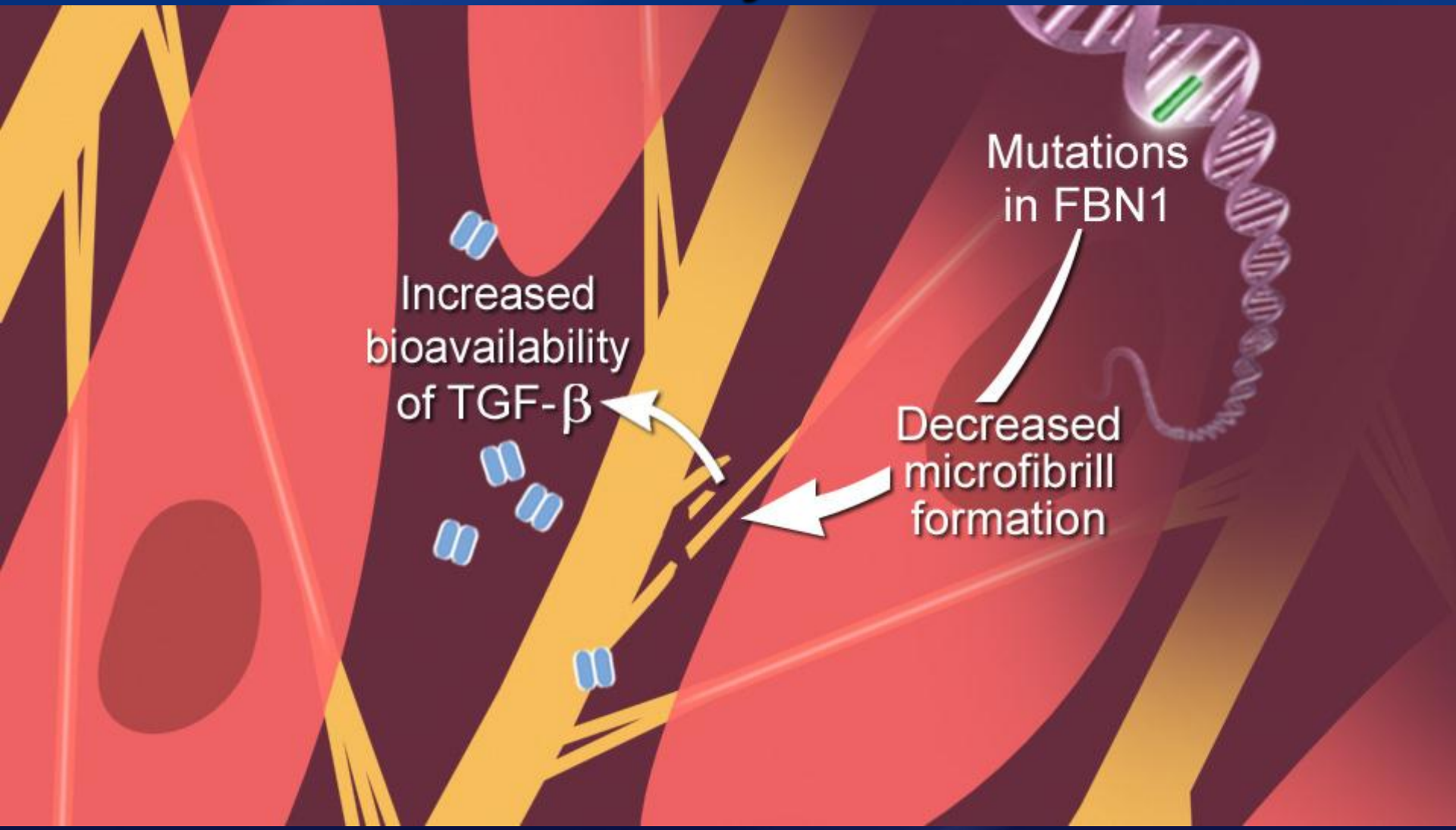
Marfan Syndrome



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Diagnosis of Marfan Syndrome Can Often be Established by Comprehensive Clinical Evaluation

Revised Diagnostic Criteria for the Marfan Syndrome

Loeys BL: J Med Genetics 2010

Ghent, Belgium

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Positive Family History of MFS
One of the Following

- Ectopia lentis
- Aortic dilatation

  Z-score ≥2 (pt ≥20 yr)

  Z-score ≥3 (pt <20 yr)
- Systemic score ≥7

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No Family History of MFS
One of the Following

- Aorta (Z-score ≥2 or dissection) + Ectopia lentis
- Aorta (Z-score ≥2 or dissection) + *FBN1* mutation
- Aorta (Z-score ≥2 or dissection) + Systemic score ≥7
- Aorta + Ectopia lentis + *FBN1* mutation

Features suggestive of other disorders must be excluded

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Systemic Score for Marfan Syndrome Diagnosis

- Wrist AND thumb sign – 3 (wrist OR thumb sign – 1)
- Pectus carinatum deformity – 2 (pectus excavatum or chest asymmetry – 1)
- Hindfoot deformity – 2 (plain pes planus – 1)
- Pneumothorax – 2
- Dural ectasia – 2
- Protrusio acetabuli – 2
- Reduced US/LS AND increased arm/height AND no severe scoliosis – 1
- Scoliosis or thoracolumbar kyphosis – 1
- Reduced elbow extension – 1
- Facial features (3/5) – 1 (dolichocephaly, enophthalmos, downslanting palpebral fissures, malar hypoplasia, retrognathia)
- Skin striae – 1
- Myopia > 3 diopters - 1
- Mitral valve prolapse (all types) – 1

Maximum total: 20 points; score ≥7 indicates systemic involvement; US/LS, upper segment/lower segment ratio.

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Loeys B et al: J Med Genetics 2010
National Marfan Foundation Website (www.marfan.org)

Acute Aortic Dissection

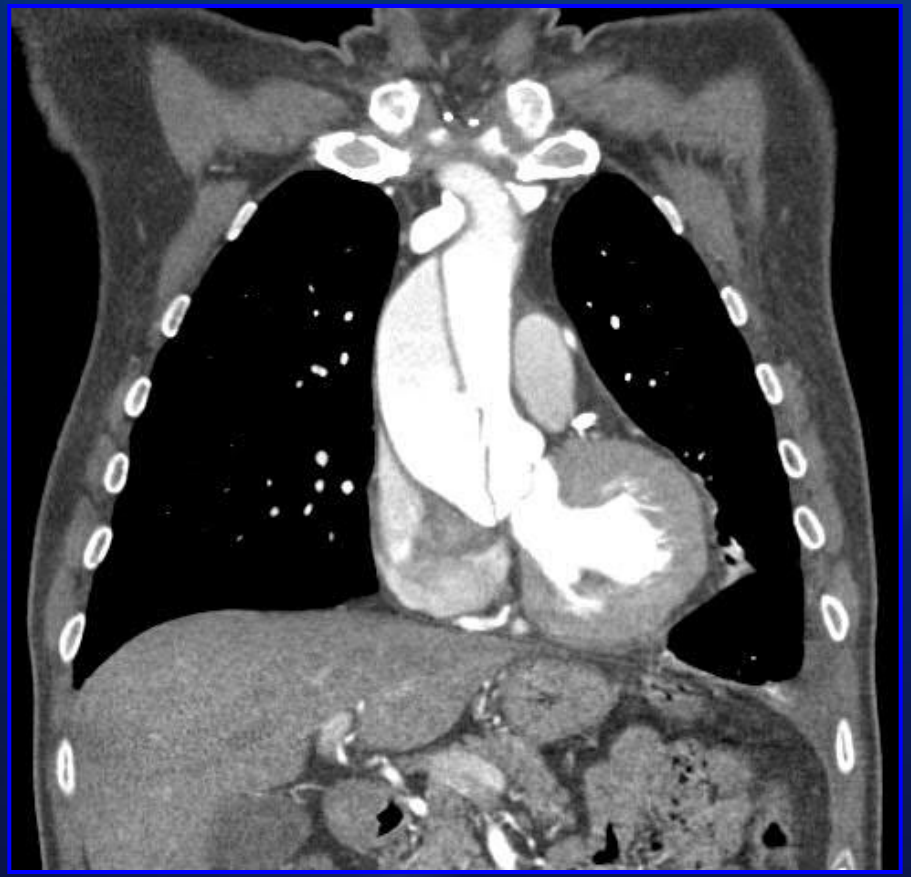
- Potentially fatal condition
- 2 - 3.5/100,000 person years
- High mortality

  40% immediate

  1% per hour – first 48 hrs

  70% - first 2 weeks
- Correct diagnosis <50%
- Goal – rapid early Dx and Rx

  Prevention



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Clinical Utility of Genetic Evaluation

- Accurate diagnosis and prognosis
- Tailor management and surveillance
- Identify pre-symptomatic individuals in affected families
- Offer reproductive options to at risk

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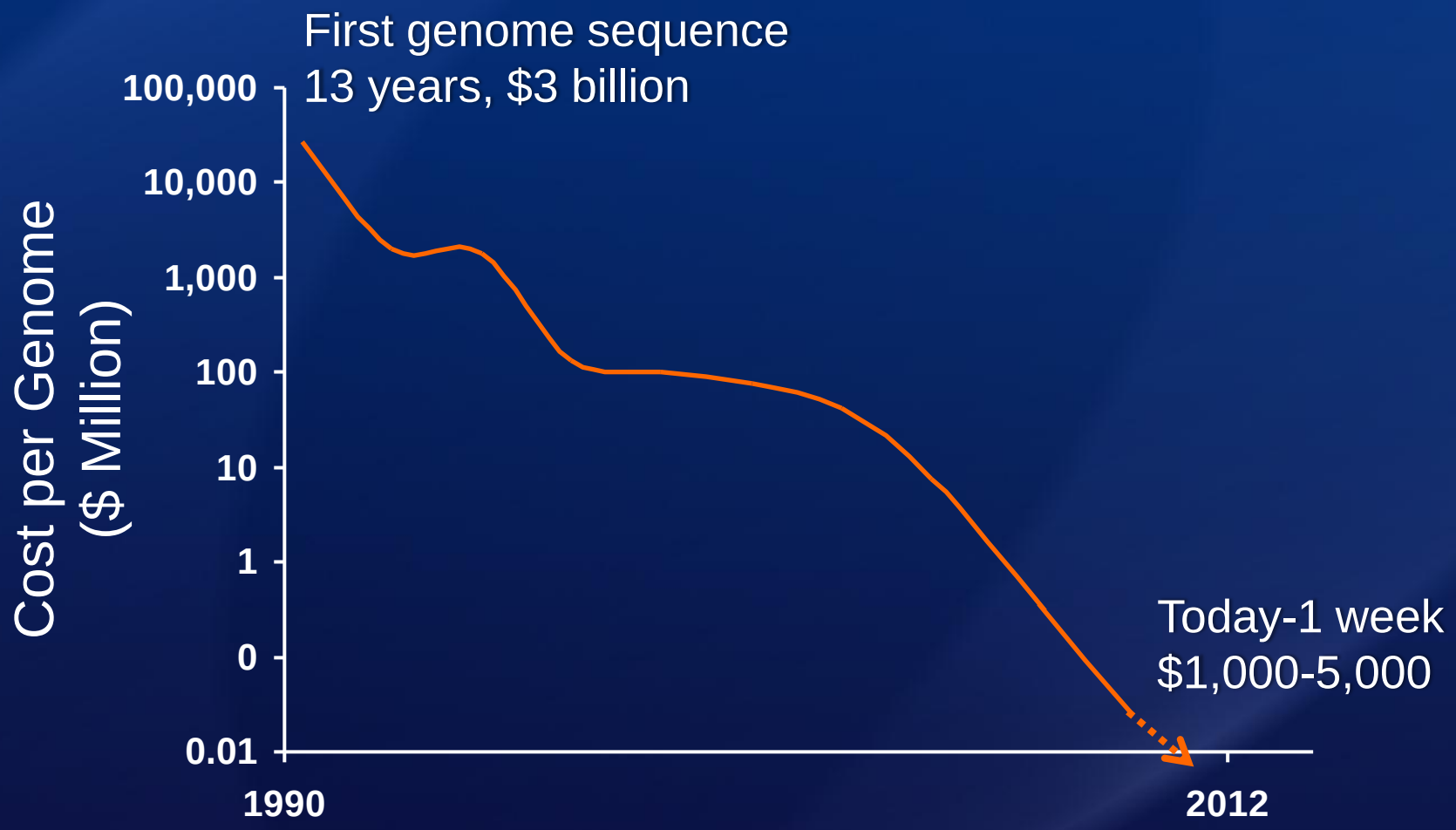
Changing Cost of DNA Sequencing



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Thoracic Aortic Aneurysms

Syndromic	**<5%**
Marfan	*FBN1*
Turner	45,X
Loeys-Dietz	*TGFBR 1, 2*
Vascular Ehlers-Danlos	*COL3A1*
Bicuspid aortic valve	***Notch-1* and ?**
Familial	**15-20%**
Sporadic	**75%**

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Syndromic

Familial

? Sporadic

Sporadic

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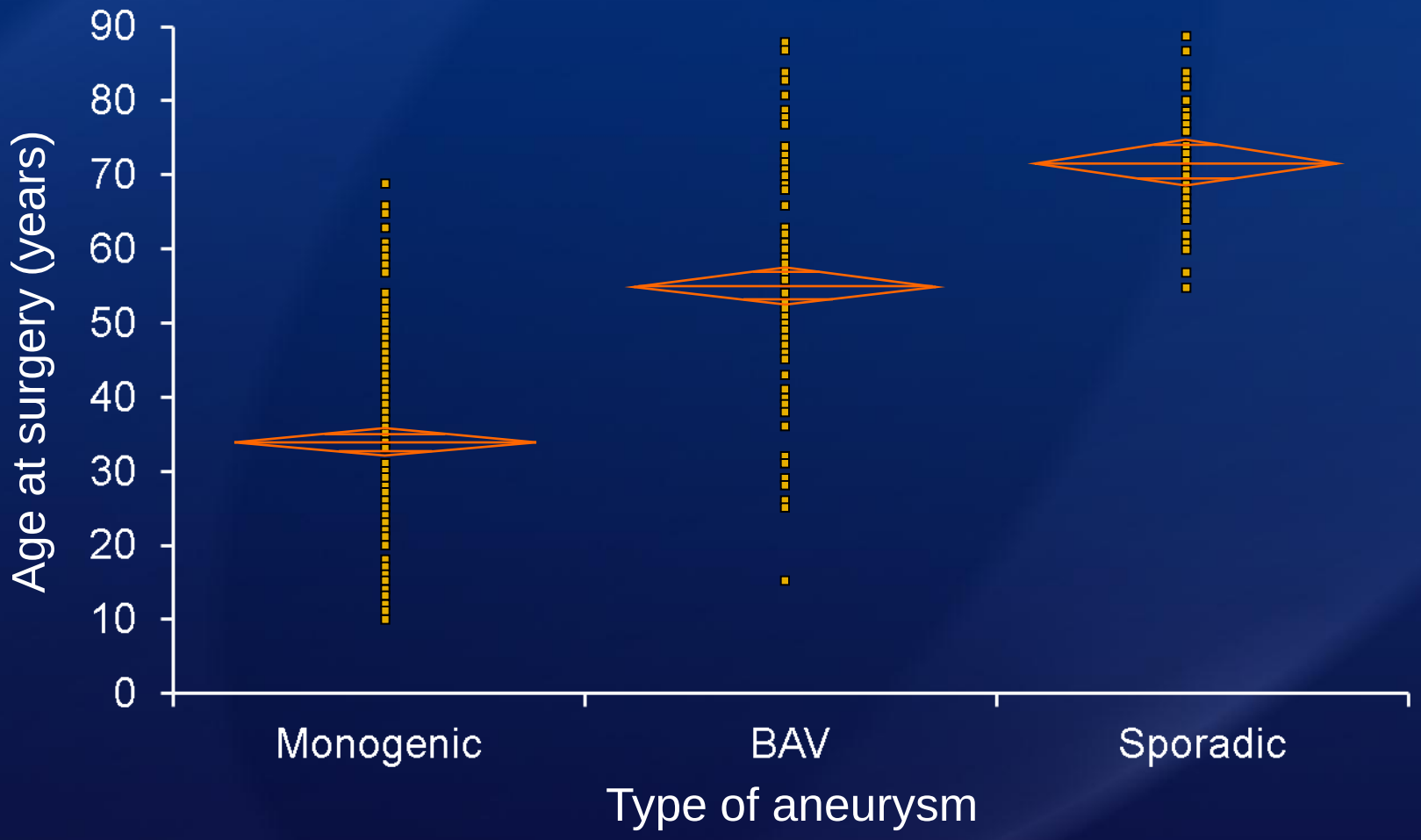
Different Groups of Patients with Thoracic Aortic Aneurysm According to Their Age at Surgery



Jondeau et al. Curr Atheroscler Rep 2012

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Examples

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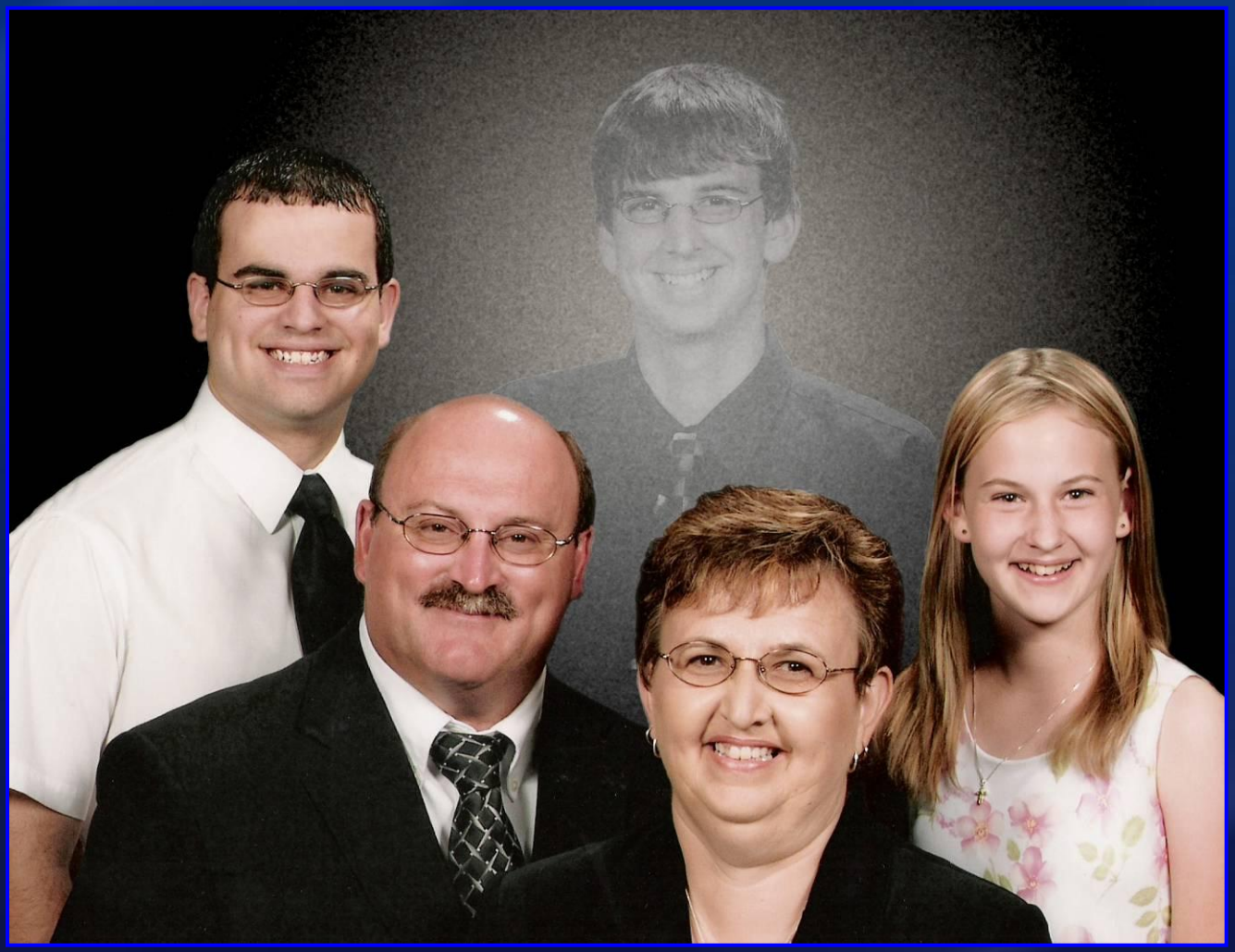

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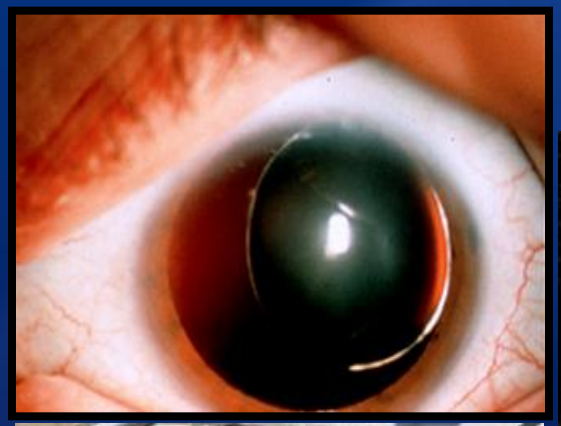
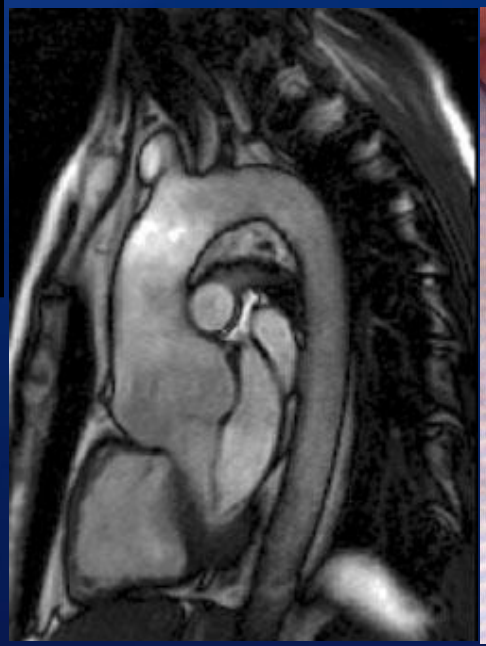
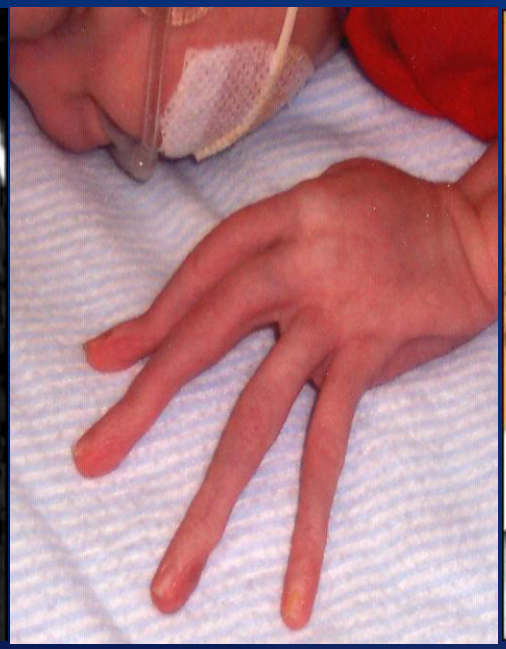
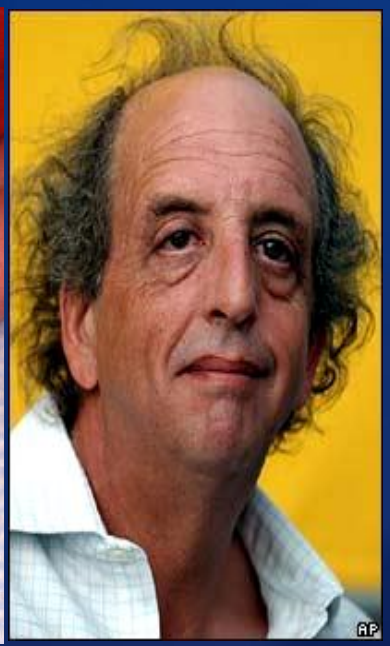
Marfan Syndrome

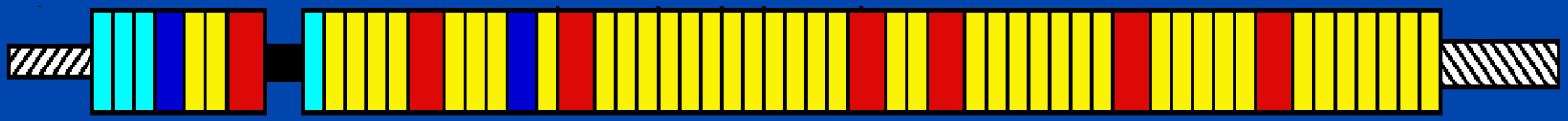








Fibrillin-1



Dietz…Francomano Nature, 1991

Pessimistic Model for Disease Pathogenesis

↓ Fibrillin-1 → Tissue Failure

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Optimistic/Current Model for Disease Pathogenesis

↓ Fibrillin-1 → Tissue Failure

+

↑ TGFβ signaling

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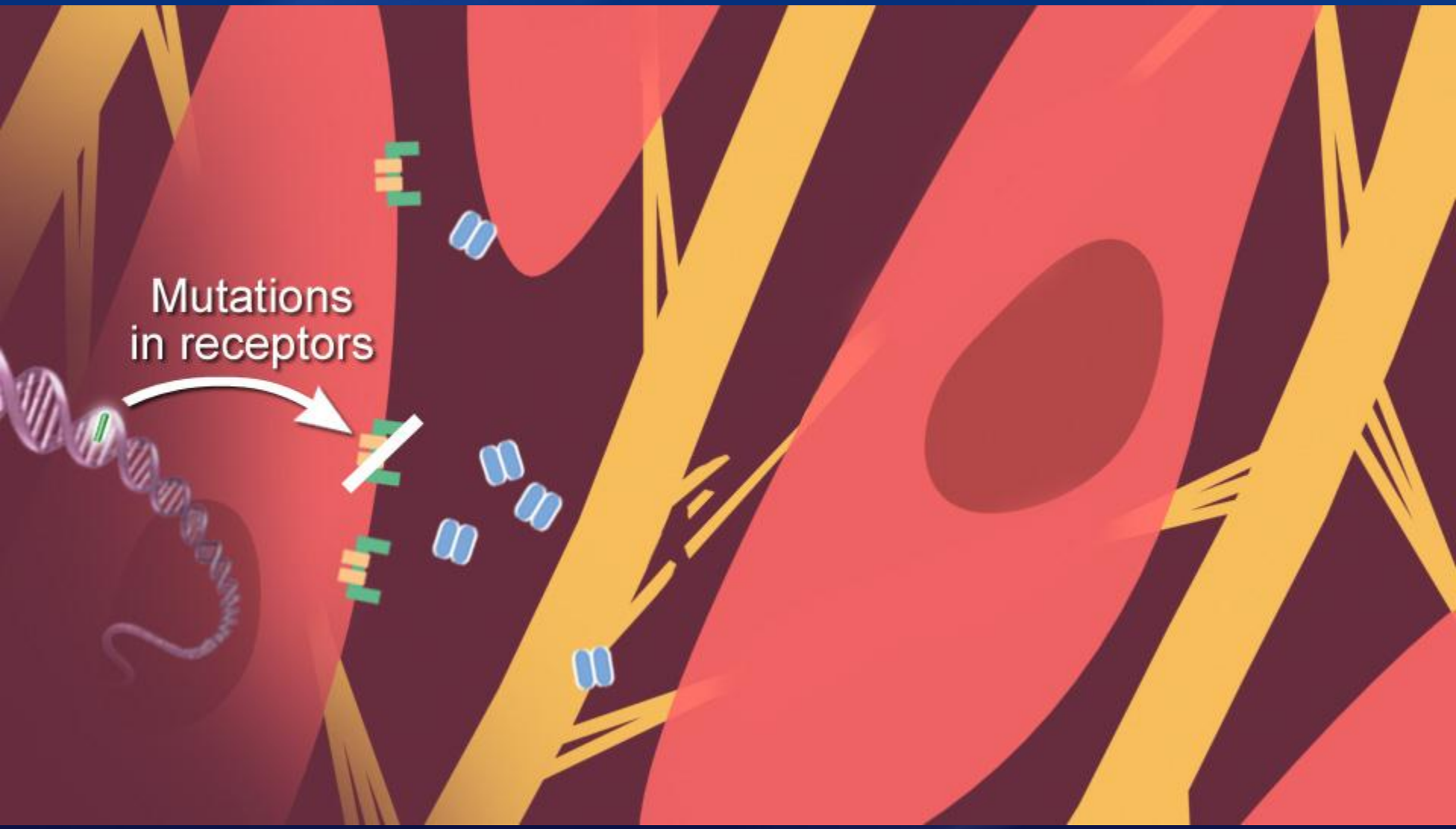
Loeys-Dietz Syndrome



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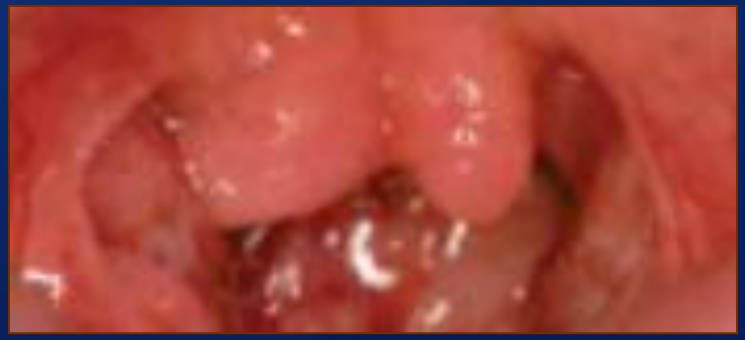
**

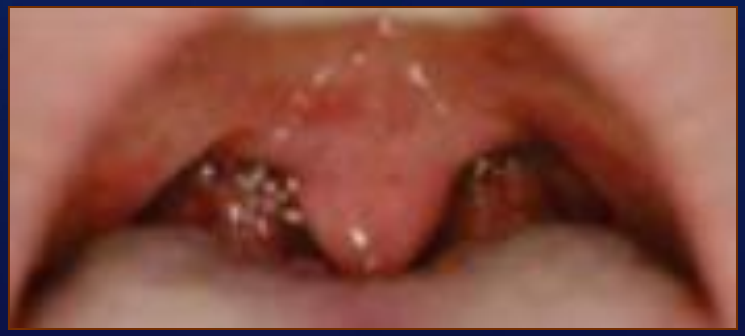
A syndrome of altered cardiovascular, craniofacial, neurocognitive and skeletal development caused by mutations in *TGFBR1* or *TGFBR2*

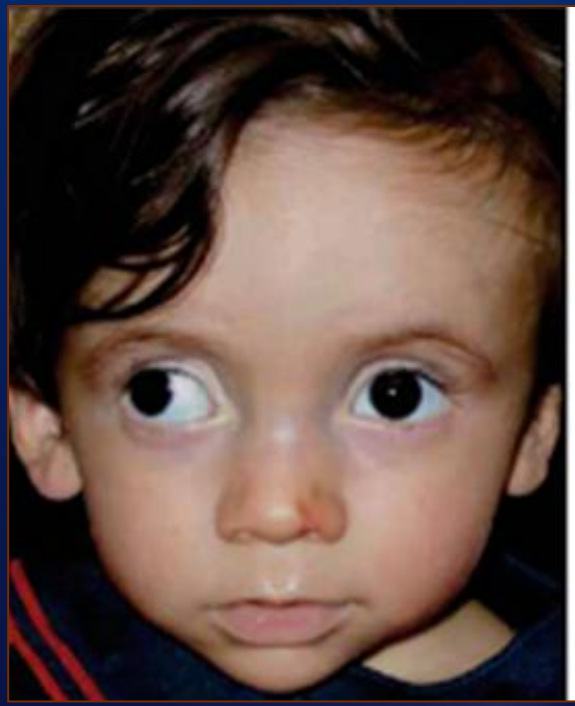
nature genetics

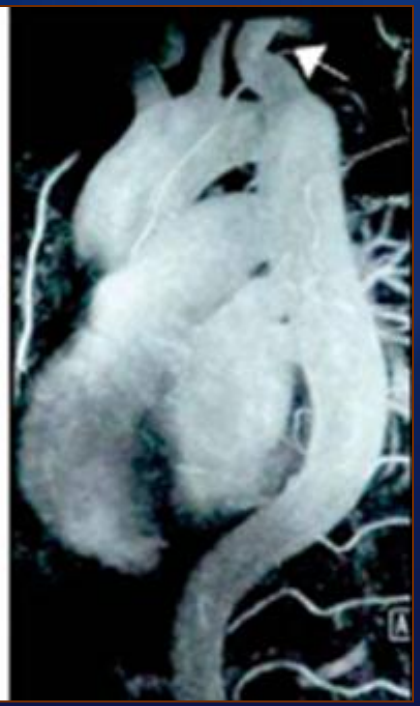
Bart L Loeys[1], Junji Chen[1,2], Enid R Neptune[3], Daniel P Judge[4], Megan Podowski[3], Tammy Holm[1], Jennifer Meyers[1,2], Carmen C Leitch[1], Nicholas Katsanis[1], Neda Sharifi[1,2], F Lauren Xu[4], Loretha A Myers[1], Philip J Spevak[5], Duke E Cameron[6], Julie De Backer[7], Jan Hellemans[7], Yan Chen[8], Elaine C Davis[9], Catherine L Webb[10], Wolfram Kress[11], Paul Coucke[7], Daniel B Rifkin[8], Anne M De Paepe[7] & Harry C Dietz[1,2]

2005









Affected Patient with Drs. Loeys and Dietz

Aggressive vascular disease

Loeys et al, NEJM 2006
Williams et al, Ann Thorac Surg 2007

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Management

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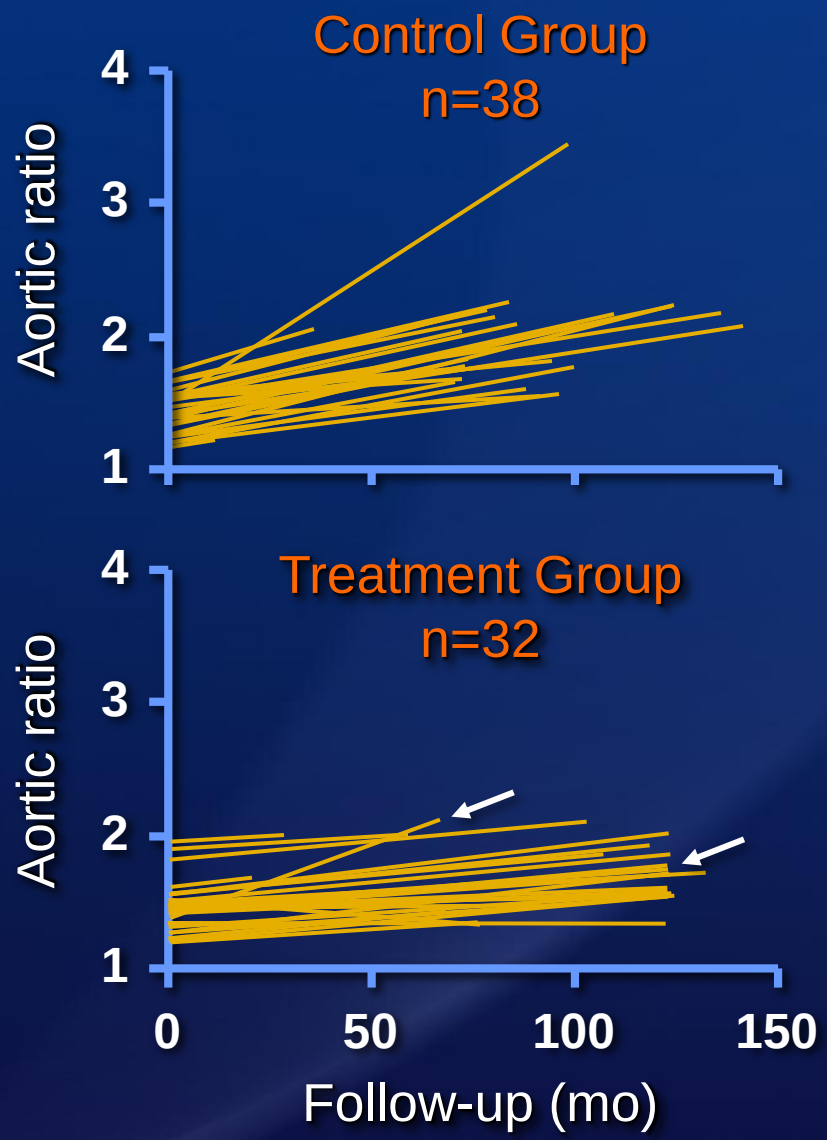
Medical Management for MFS

Shores: NEJM, 1994

- Propranolol in MFS
- β blockers
  - ↓ HR and LV ejection
  - ↓ aortic root dilation
  - ↓ CV complications



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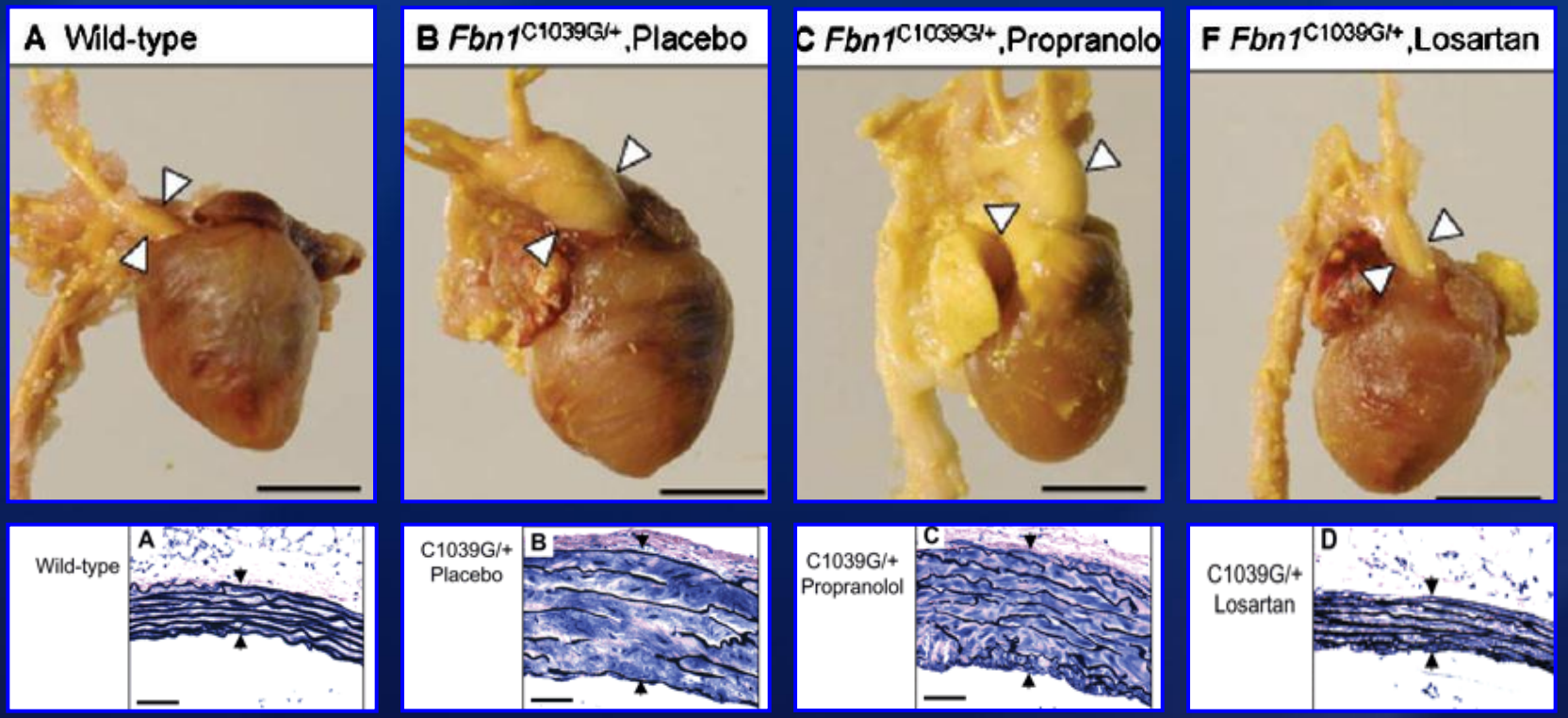
Mouse Model MFS and Losartan



Losartan treated mouse – normal aortic development

Habashi, Dietz et al: Science 2006

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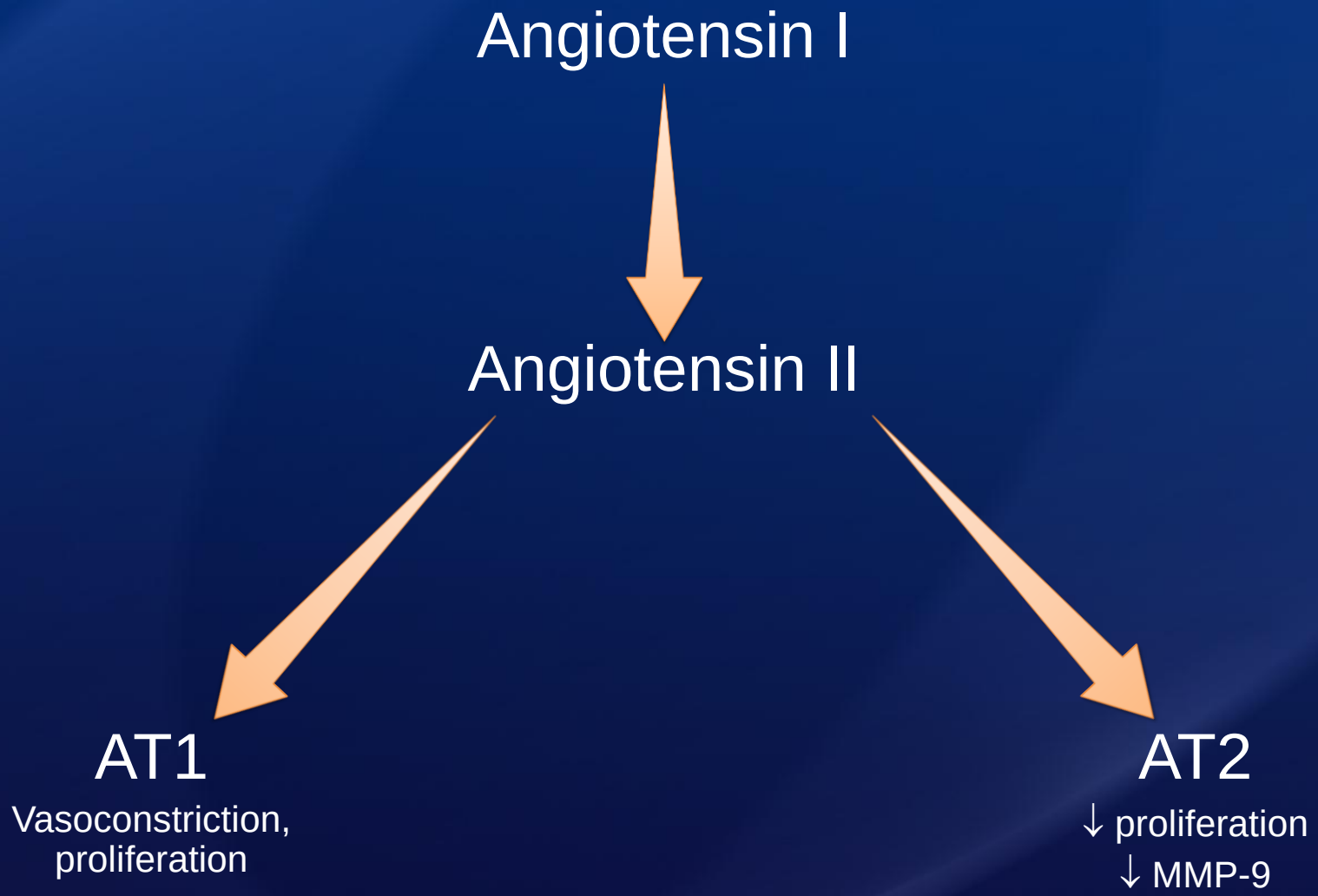
ACE or ARB in MFS?



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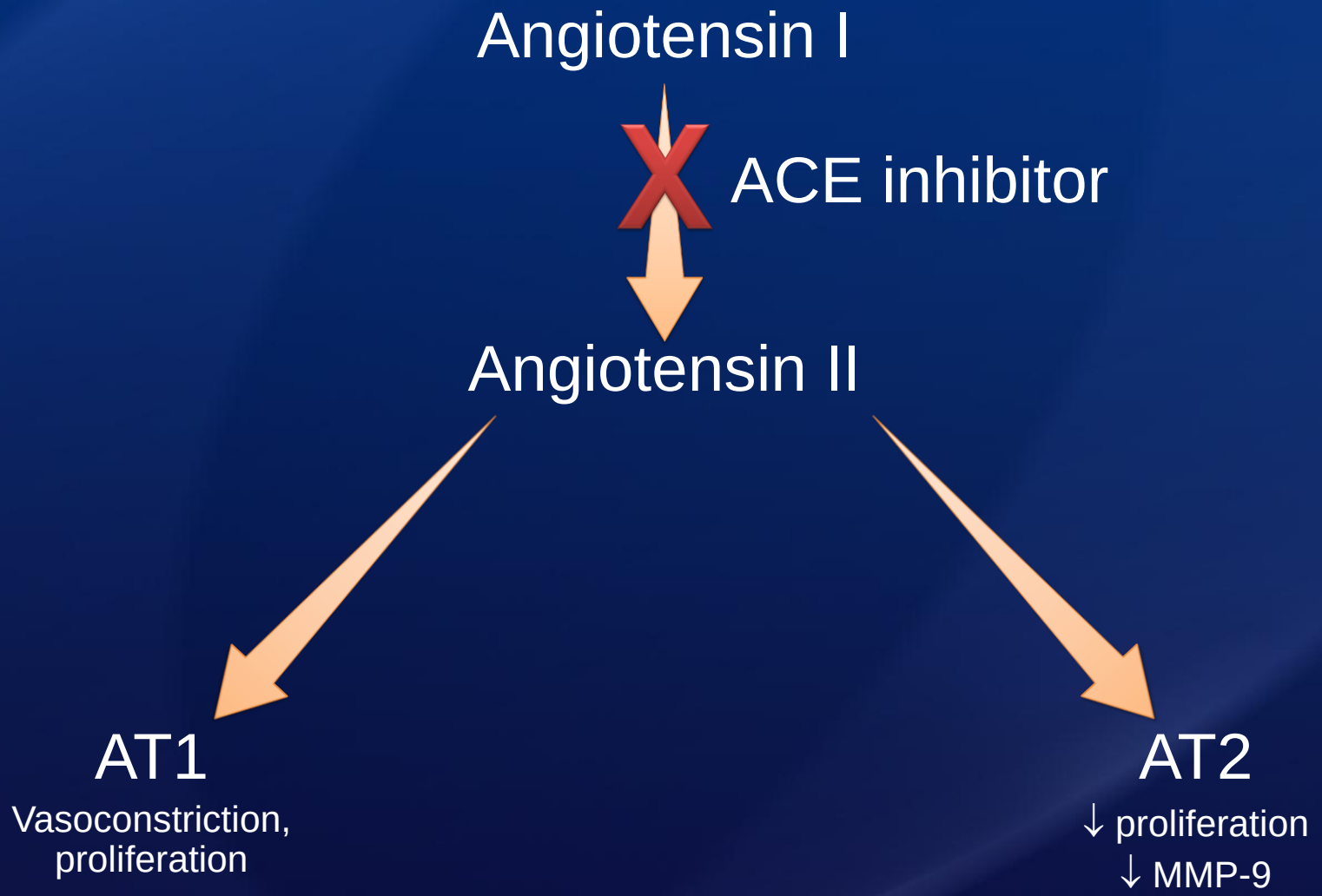

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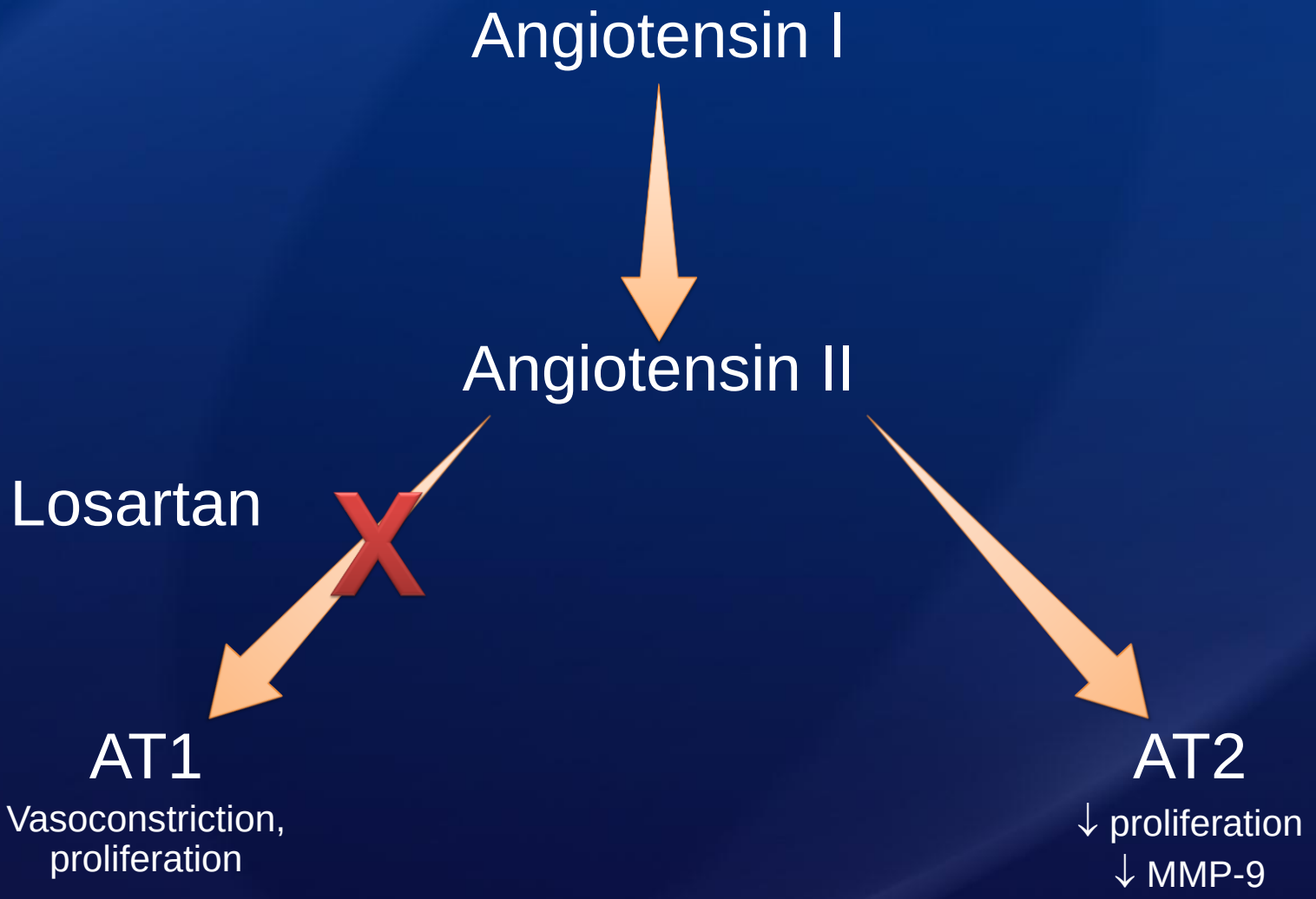

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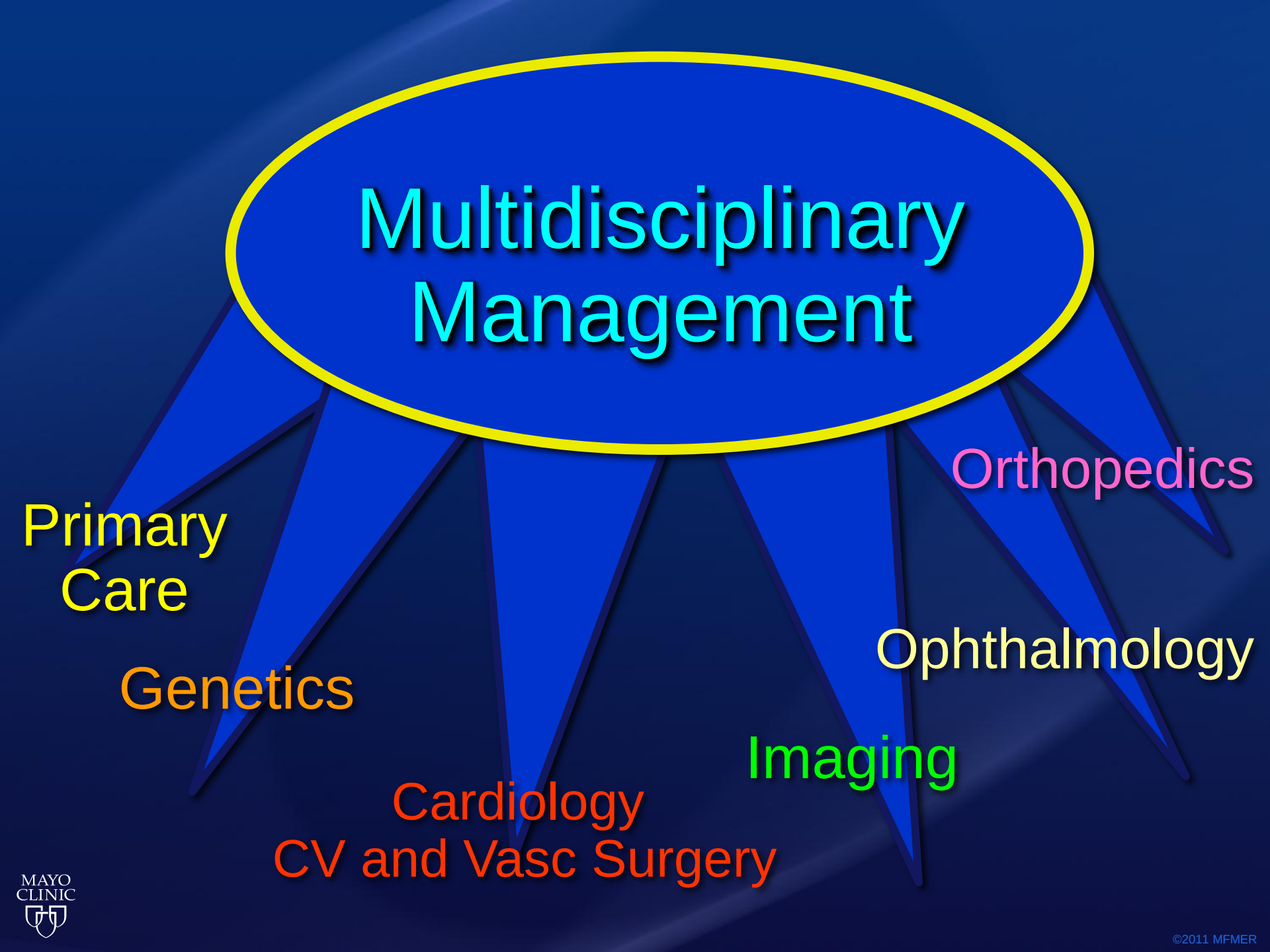

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Indications for Operation MFS

Asc ao size
45-50 mm

Rapid ↑
>5 mm/yr

Family history of aortic complications

Small pt - indexed diameter adjusted for BSA of 2.75 cm/m2
Should be considered for operative decision making

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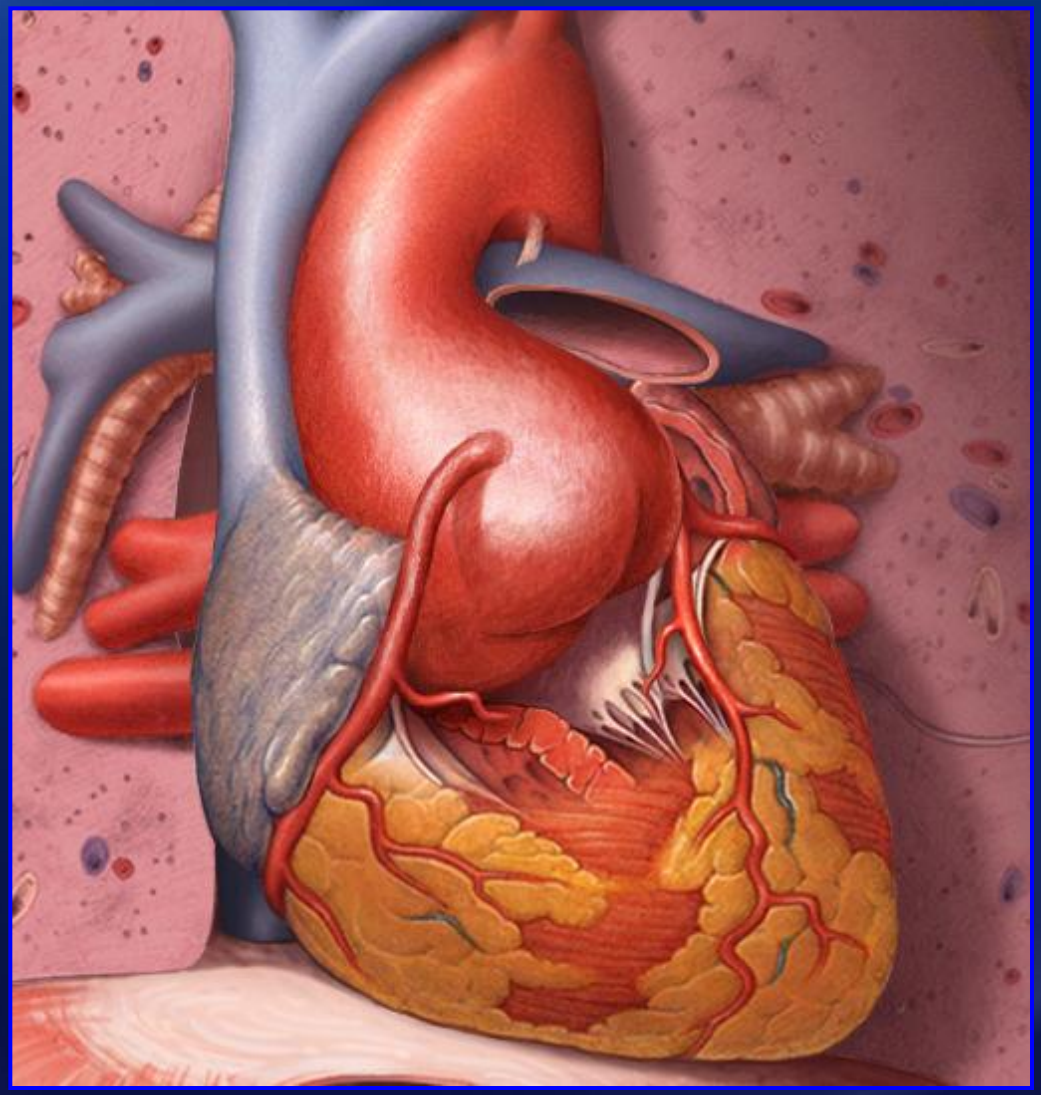

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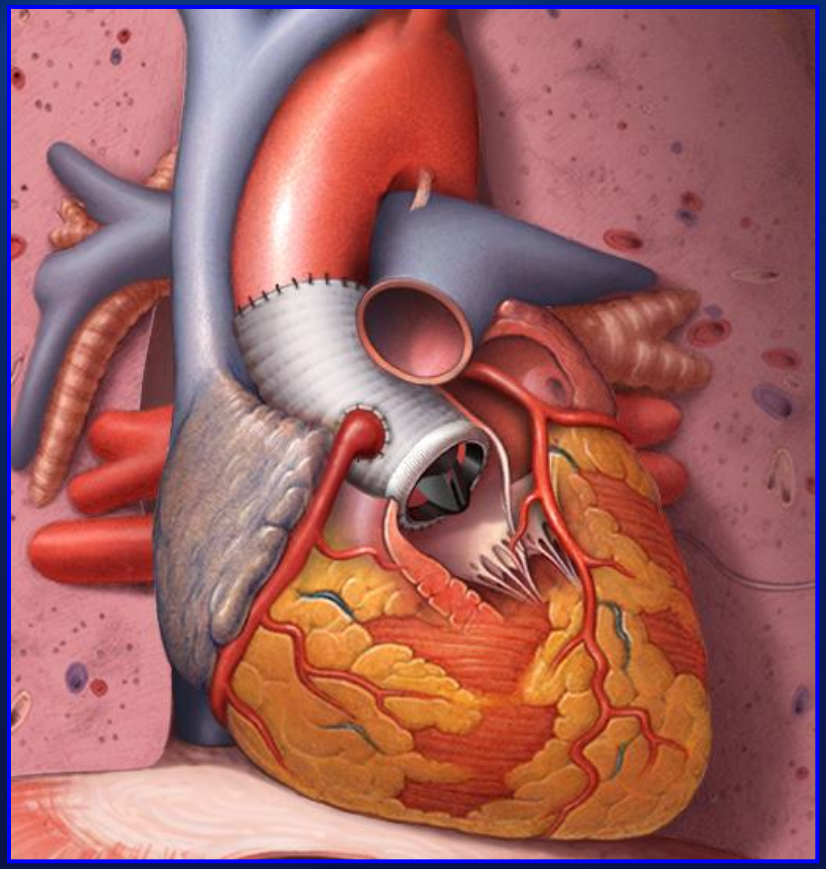
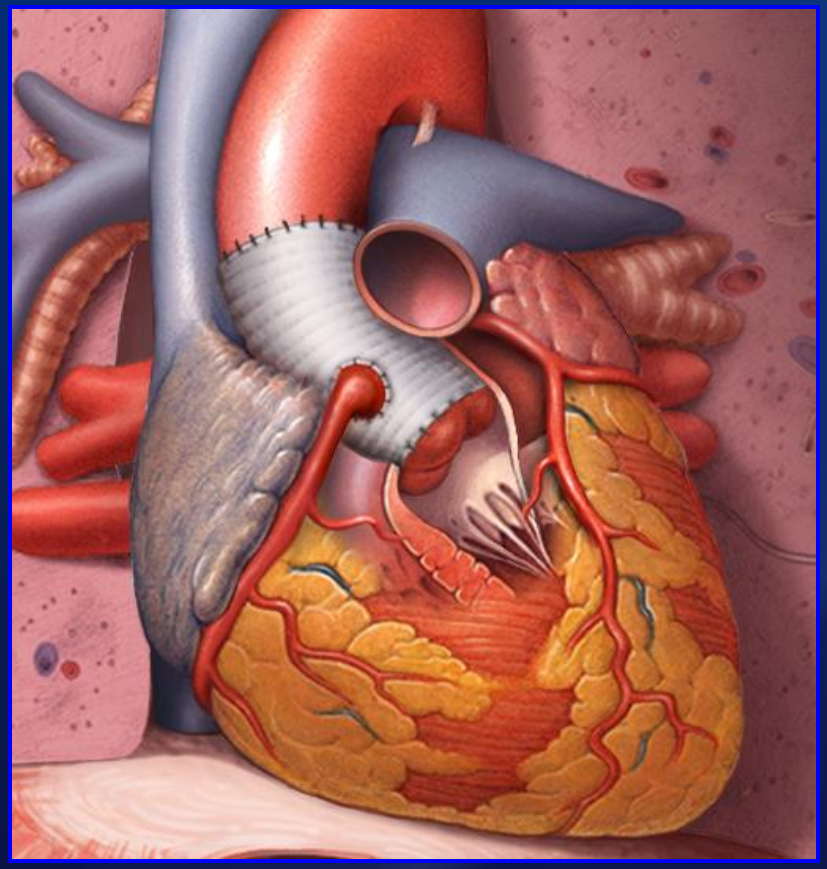
Bentall Operation



Valve Sparing Operation



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Others

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70-Year-Old Man with Hypertension

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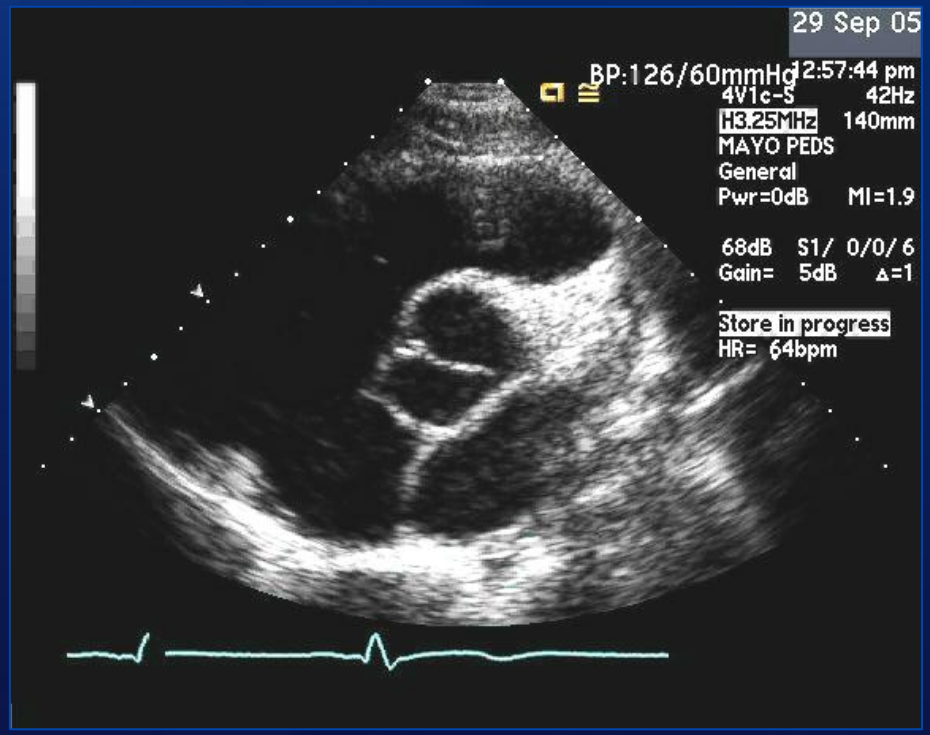
45-Year-Old Man - Bicuspid AV

BAV Related Aortopathy



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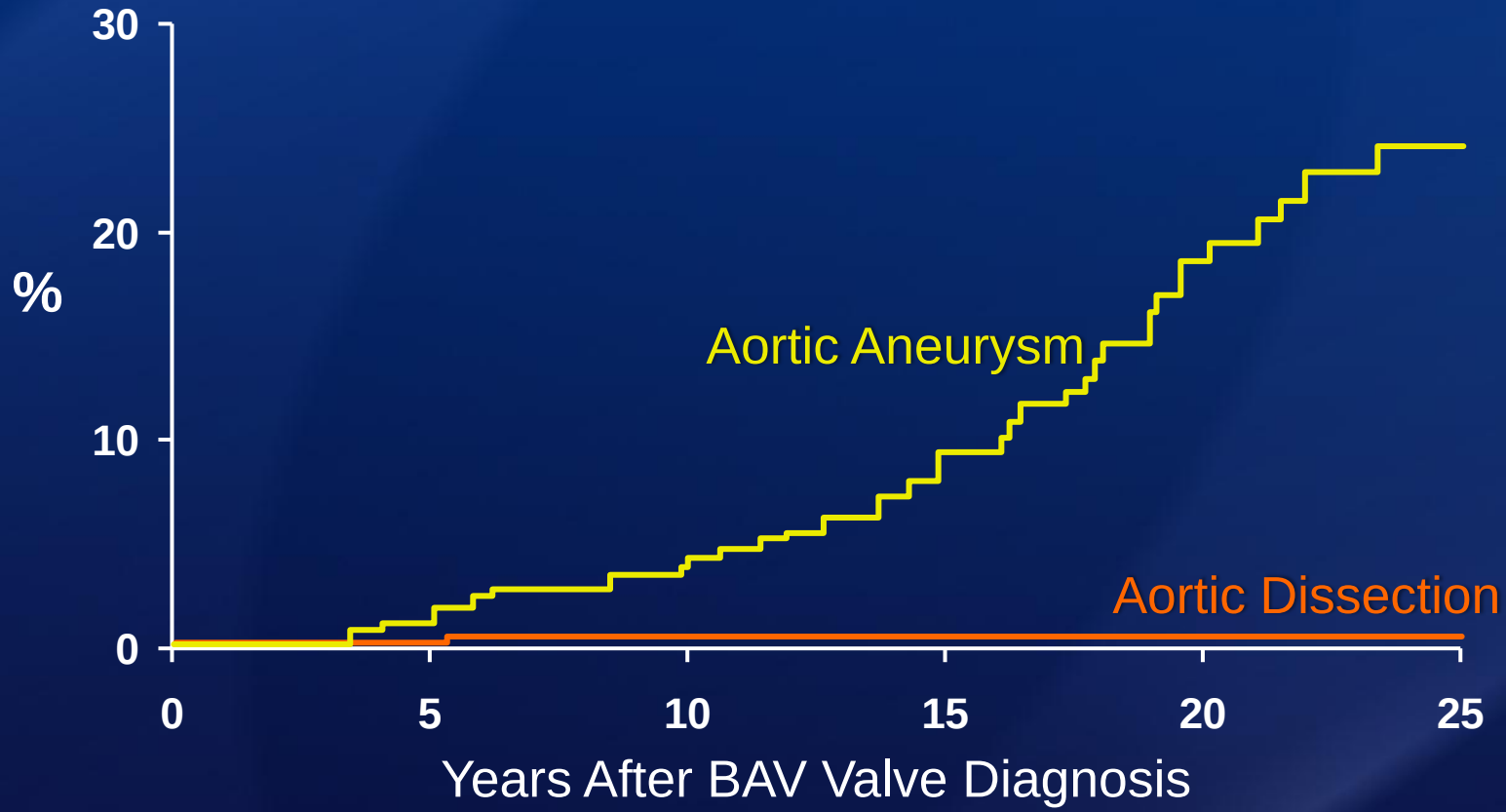
Risk of Aneurysm Formation and Dissection After BAV Diagnosis



No. at Risk						
Ao Aneurysm	384	352	309	186	88	39
Ao dissection	416	387	348	209	110	53

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Michelena et al: JAMA, 2011

Family Screening

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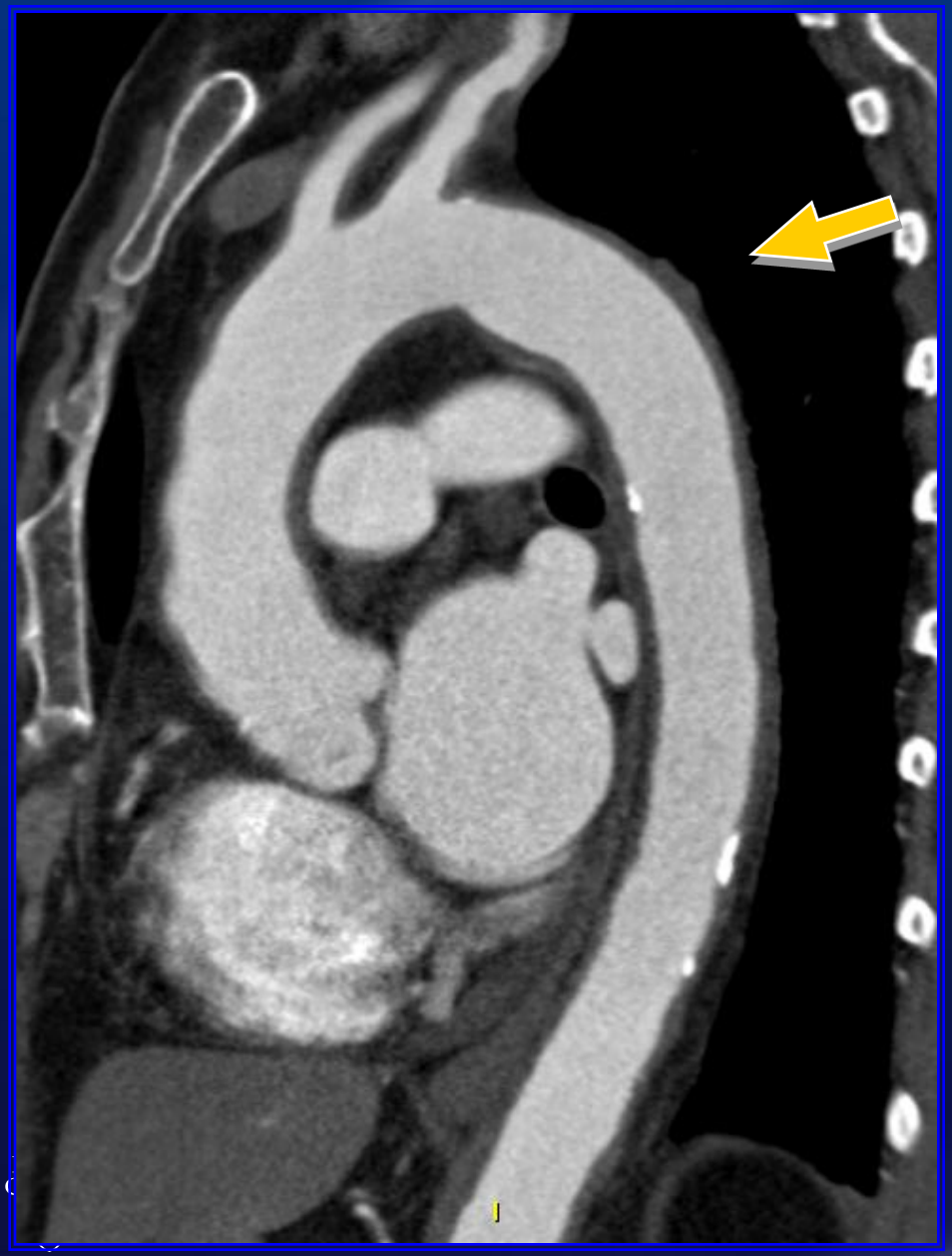
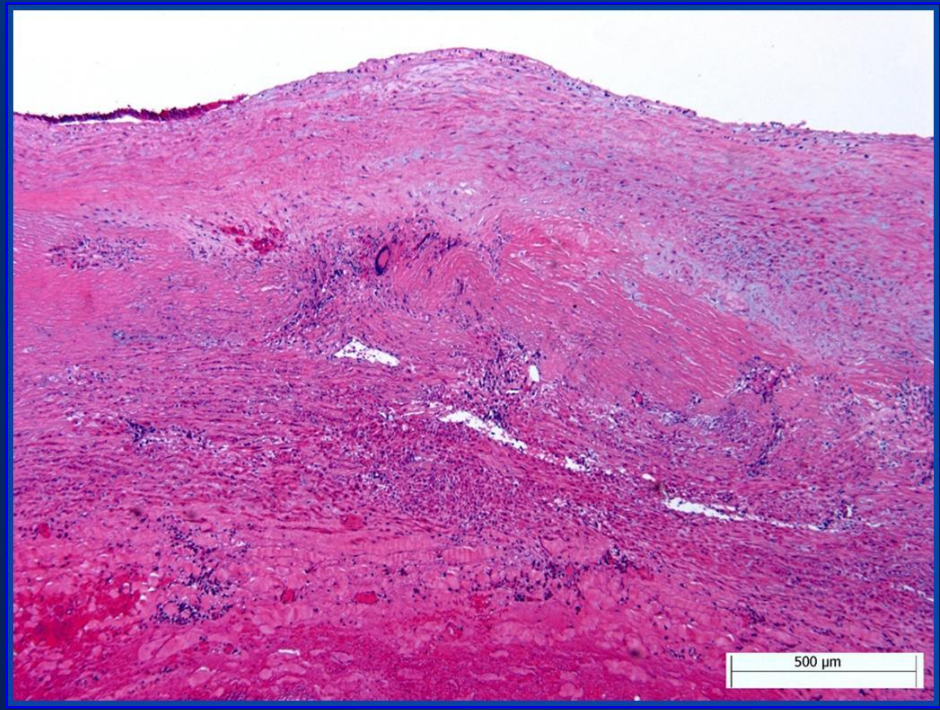
Active Giant Cell Aortitis





Evans J et al: Ann Internal Medicine 1995
Agard C et al: Arthritis Rheum 2008

Summary – Thoracic Aortic Aneurysms

- Past

  Limited diagnostic paradigm

  Crisis-driven management

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Summary – Thoracic Aortic Aneurysms

- Past
  - Limited diagnostic paradigm
  - Crisis-driven management
- Present
  - More effective diagnostic paradigms
  - Medical management options
  - Safe interventions

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Summary – Thoracic Aortic Aneurysms

- Past
  - Limited diagnostic paradigm
  - Crisis-driven management
- Present
  - More effective diagnostic paradigms
  - Medical management options
  - Safe interventions
- Future
  - Specific genetic diagnosis in each patient
  - Management directed by genetic diagnosis

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Take Home Points - Marfan

1. Don’t miss clues to diagnosis of Marfan – you can save a life with an Echo/CT/MR!
2. Multimodality imaging imperative
3. Elective operation when asc aorta ≥50 mm, smaller in some
4. Life-long multidisciplinary follow-up

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Questions or Comments?

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