Connective Tissue Disorders for the Vascular Surgeon: *Lessons Learned at Hopkins*

James H. Black, III, MD, FACS
The David Goldfarb, MD, Research Professor of Surgery

Chief, Division of Vascular Surgery and Endovascular Therapy
The Johns Hopkins Hospital, Baltimore, Maryland

Annual Scientific Meeting
Vascular Society
28 Nov 2018

JOHNS HOPKINS
MEDICINE

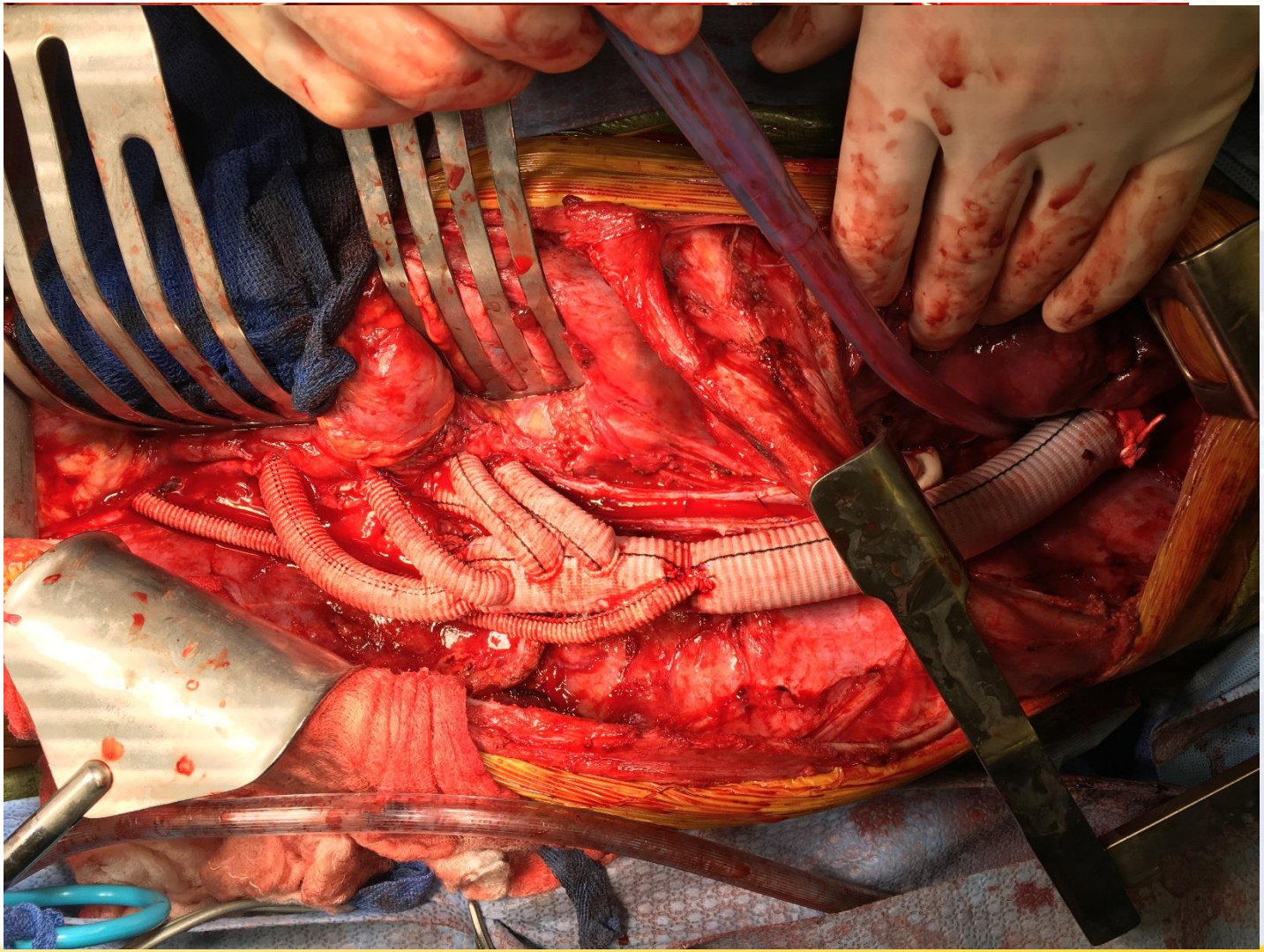
Rational Empiricism of Osler

"There is no disease more conducive to clinical humility than aneurysm of the aorta."

"The tragedies of life are largely arterial."

JOHNS HOPKINS
MEDICINE

- 12 year old Loeys-Dietz Syndrome….



JOHNS HOPKINS MEDICINE

Connective Tissue Disorders

- Primary target are structural proteins composed of elastin and collagen (not CVD)

Structural Elements of Blood Vessels

Structural Proteins	Approximate Amount (% dry wt)	Function
Type I Collagen	20-40	Fibrillar net
Type III Collagen	10-20	Thin fibrils
Elastin, fibrillin	20-40	Elasticity
Type IV Collagen, Laminin	<5	Basilar
Type V and VI Collagen	<2	Unclear
Proteoglycans (>30 types)	<3	Resilience

- COL3 is very important in vasculogenesis.

JOHNS HOPKINS MEDICINE

What Are Connective Tissue Disorders?

1. Studied natural history
2. Defined basis for genetic inheritance
3. Understood pathophysiologic mechanism to guide treatment

"***Heritable Disorders of Connective Tissue***"

Victor McCusick, MD, 1952

Marfan Syndrome

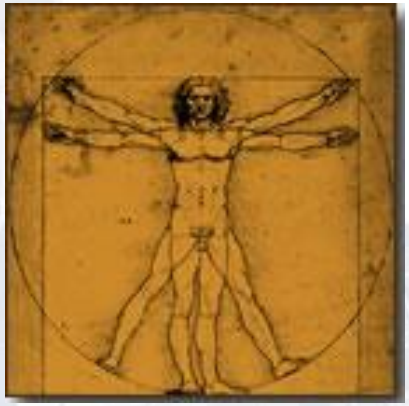
Vascular Ehlers Danlos Syndrome

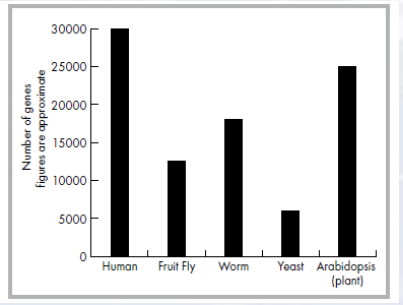
Loeys-Dietz Syndrome

JOHNS HOPKINS MEDICINE

A Brief History of Progress…

- Technological advances set the stage for rapid sequencing technology.
- Human Genome Project:
  - Started 1990
  - **The DNA sequence of human chromosome 22**
  - Full sequence of C22, December 1999.
    - 33,000,000 bp, approximate 550 genes.
  - Completed April, 2003.
    - 30,000 total genes.
  - Only 380 have been linked to disease.





JOHNS HOPKINS MEDICINE

Genetics Influences on Aneurysms

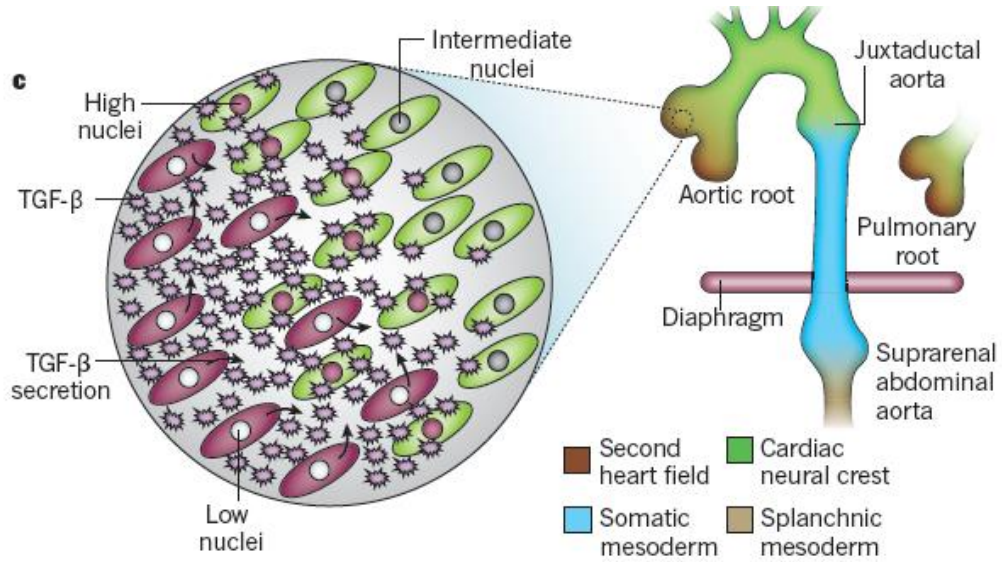
Gene (protein)	Human aneurysmal syndrome
Extracellular matrix protein	
FBN1 (fibrillin-1)	MFS; highly penetrant ascending aortic aneurysm
EFEMP2 (fibulin-4)	Cutis laxa with aneurysm; ascending aortic aneurysm and tortuosity
ELN (elastin)	Cutis laxa with aneurysm; low penetrance ascending aortic aneurysm and dissection
COL1A1 (collagen α-1(I))	Osteogenesis imperfecta; extremely rare aortic aneurysm; EDS, type 7A; dissection of medium-sized arteries
COL1A2 (collagen α-2(I))	Osteogenesis imperfecta; extremely rare aortic aneurysm; EDS, cardiac valvular dystrophy type 7B; borderline aortic root enlargement with aortic regurgitation
COL3A1 (collagen α-1(III))	EDS, type 4; frequent arterial dissection with infrequent aneurysm
COL4A1 (collagen α-1(IV))	Hereditary angiopathy, nephropathy, aneurysms and muscle cramps; infrequent aneurysms
COL4A5 (collagen α-5(IV))	X-linked Alport syndrome; ascending aortic and abdominal aneurysms and dissections
LOX (lysyl oxidase)	No human phenotype described
PLOD1 (lysyl hydroxylase 1)	EDS, type 6; rare aneurysm
PLOD3 (lysyl hydroxlase 3)	Bone fragility with contractures, arterial rupture and deafness; frequent medium-sized arterial aneurysms
Transmembrane protein	
TGFBR1 (TGF-β receptor type 1)	LDS; highly penetrant root and diffuse large and medium arterial aneurysms
TGFBR2 (TGF-β receptor type 2)	LDS; highly penetrant root and diffuse large and medium arterial aneurysms; familial thoracic aortic aneurysms and dissections; highly penetrant root and medium arterial aneurysms
ENG (endoglin)	Hereditary haemorrhagic telangiectasia; incompletely penetrant aortic and medium-sized arterial aneurysms
ACVRL1 (activin receptor-like kinase I)	Hereditary haemorrhagic telangiectasia; incompletely penetrant aortic and medium-sized arterial aneurysms
SLC2A10 (glucose transporter type 10)	Arterial tortuosity syndrome; diffuse arterial tortuosity, stenoses, aneurysms
NOTCH1 (NOTCH1)	Bicuspid valve with ascending aortic aneurysm
JAG1 (JAGGED1)	Alagille syndrome; intracranial aneurysms, coarctation of the aorta, aortic aneurysm
GJA1 (connexin-43)	Hypoplastic left heart syndrome (HLHS)

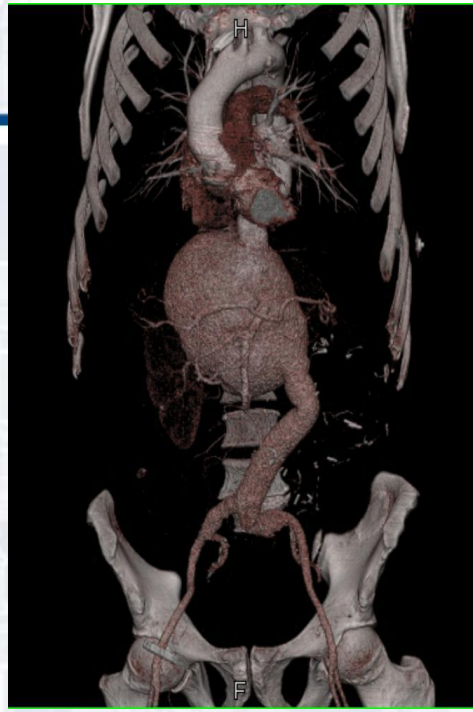
Gene (protein)	Human aneurysmal syndrome
Transmembrane protein cont.	
PKD1 (polycystin-1)	Polycystic kidney disease with intracranial aneurysms
PKD2 (polycystin-2)	Polycystic kidney disease with intracranial aneurysms
Cytoplasmic protein	
SMAD3 (SMAD family member 3)	LDS; aortic aneurysm with osteoarthritis
ACTA2 (α-smooth muscle actin)	Familial aortic aneurysm with livedo reticularis and iris flocculi
MYH11 (smooth muscle myosin)	Familial aortic aneurysm with patent ductus arteriosus
FLNA (filamin-A)	Periventricular nodular heterotopia with EDS features; ascending aortic aneurysm and valvular dystrophy
NF1 (neurofibromin-1)	Neurofibromatosis; medium-sized arterial aneurysm and stenosis
PTPN11 (protein-tyrosine phosphatase 2C)	Noonan and LEOPARD syndromes; coronary artery aneurysms and rare ascending aortic aneurysm
NPHP3 (nephrocystin-3)	Nephronophthisis
NOS3 (nitric oxide synthase 3)	Refractory hypertension
TSC2 (tuberin)	Tuberous sclerosis; diffuse thoracoabdominal aneurysms
GAA (lysosomal α-glucosidase)	Acid maltase deficiency, adult onset; intracranial aneurysms
S100A12 (S100A12)	No human phenotype; increased S100A12 protein expression in human *MYH11*-mutation aneurysmal tissues
Nuclear protein	
MED12 (mediator complex subunit 12)	Lujan–Fryns syndrome; extremely rare aneurysm
KLF15 (Krüppel-like factor 15)	No human phenotype; Krüppel-like factor 15 downregulated in human abdominal aortic aneurysm
KLF2 (Krüppel-like factor 2)	No human phenotype
Chromosomal anomaly	
45, X	Turner syndrome; bicuspid aortic valve, coarctation of the aorta, ascending aneurysm

Doyle, FEBS letters, 2012

JOHNS HOPKINS MEDICINE

Cell Biology of the Aorta *in utero*

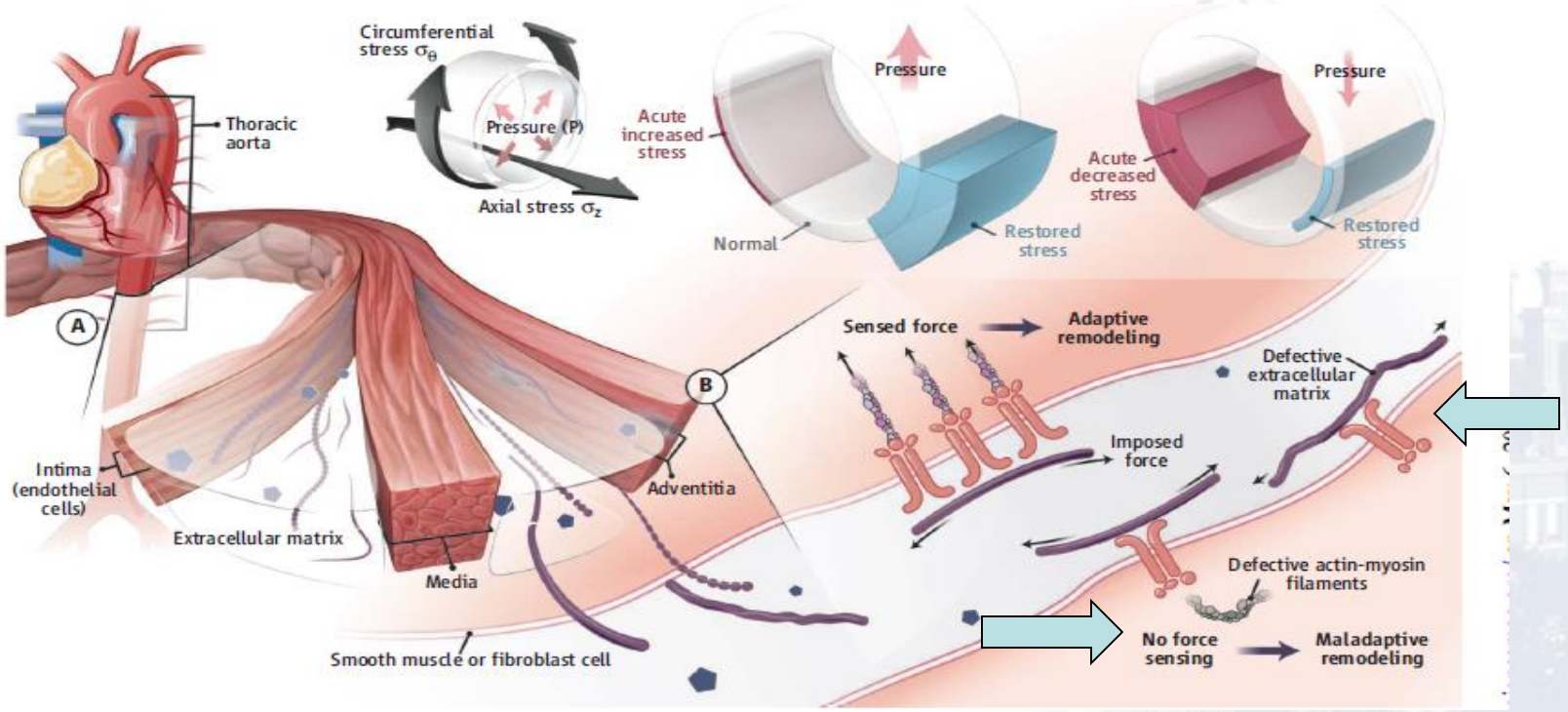




- Vasculogenesis vs Elastogenesis.
- Different lineages have different biologies.
- Very likely to respond differently to physical and environmental stressors.
- Obligate failures of CTD?

JOHNS HOPKINS MEDICINE

Reconciling Dissection and Aneurysm Pathophysiology…..



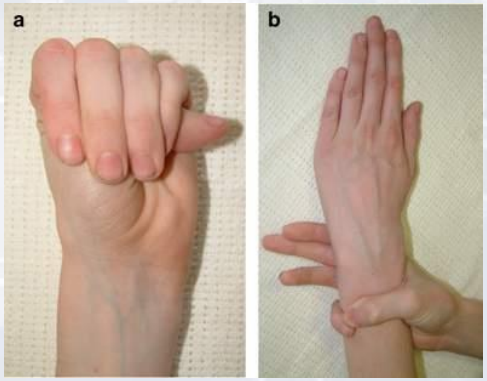
Aortic biology is a now realized as marriage of matrix homeostasis and structural stressors.

Lindsey, Dietz, Nature 2013
Humphrey, Science, 2015

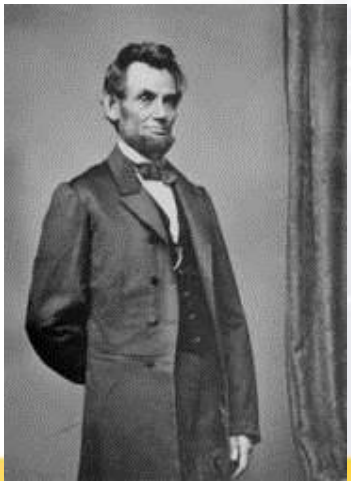
JOHNS HOPKINS MEDICINE

Diagnosis of MFS

- Revised in 2012
  - More emphasis on cardinal features of root aneurysm and lens dislocation
  - FBN1 testing weighted with a score of other systemic findings



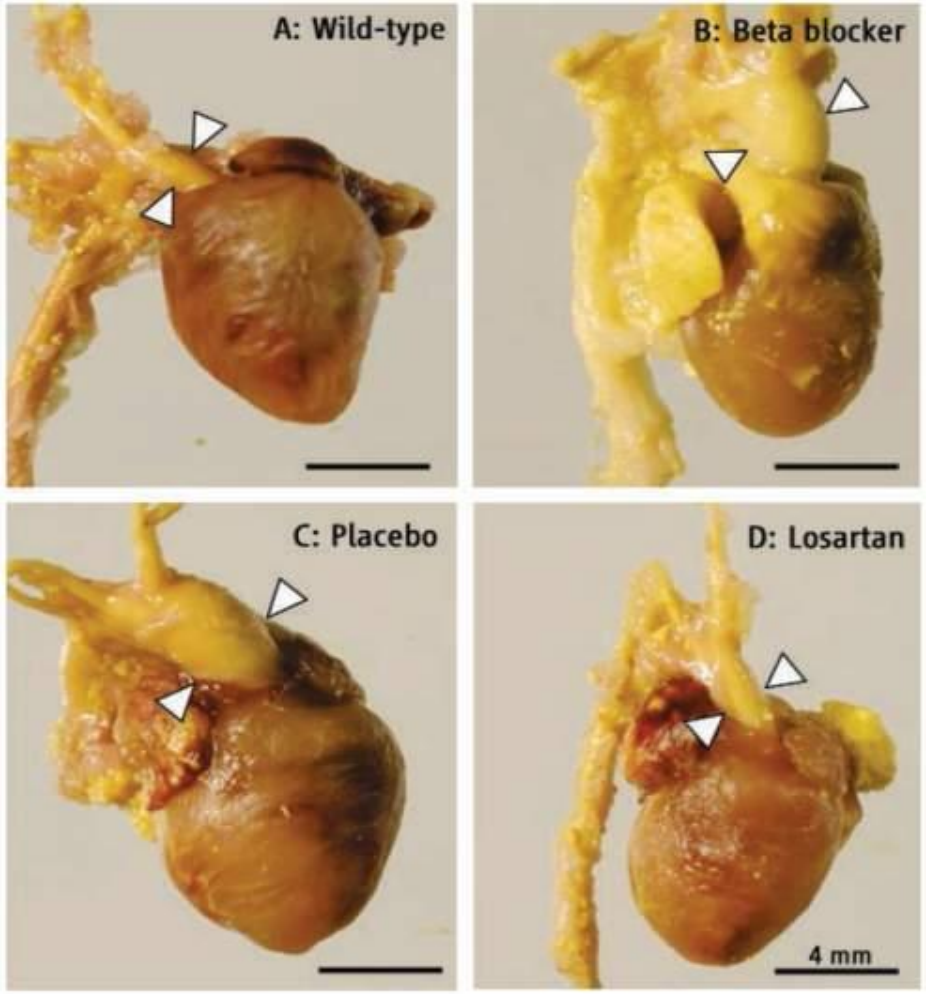
- Differential diagnosis is MASS, LDS, CCA
- ß-blocker ± ARB (Lacro, NEJM)



JOHNS HOPKINS MEDICINE

Surveillance and Management

- Pleiotropi[c] s at risk
  - www.ma[rfan.org]
  - Yearly e[cho]
- Beta-bloc[kade] n (NEJM, 2007).
  - Lowering[BP] d aortic root growth ra[te]
- Lifestyle m[odification] rcise
  - 40% dea[th] CV disease
  - Avoidan[ce] ady effort
  - 50% incr[ease] m

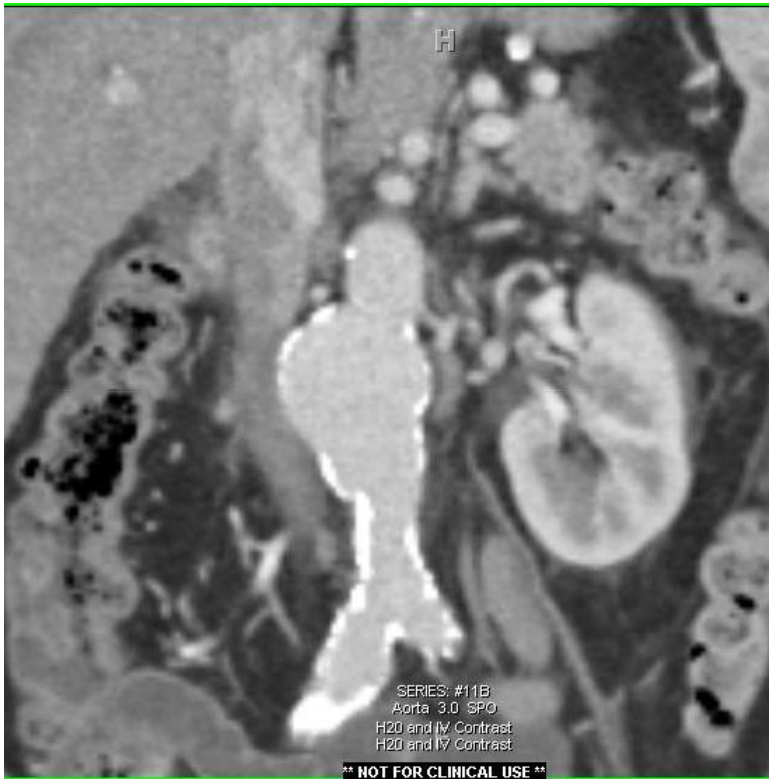


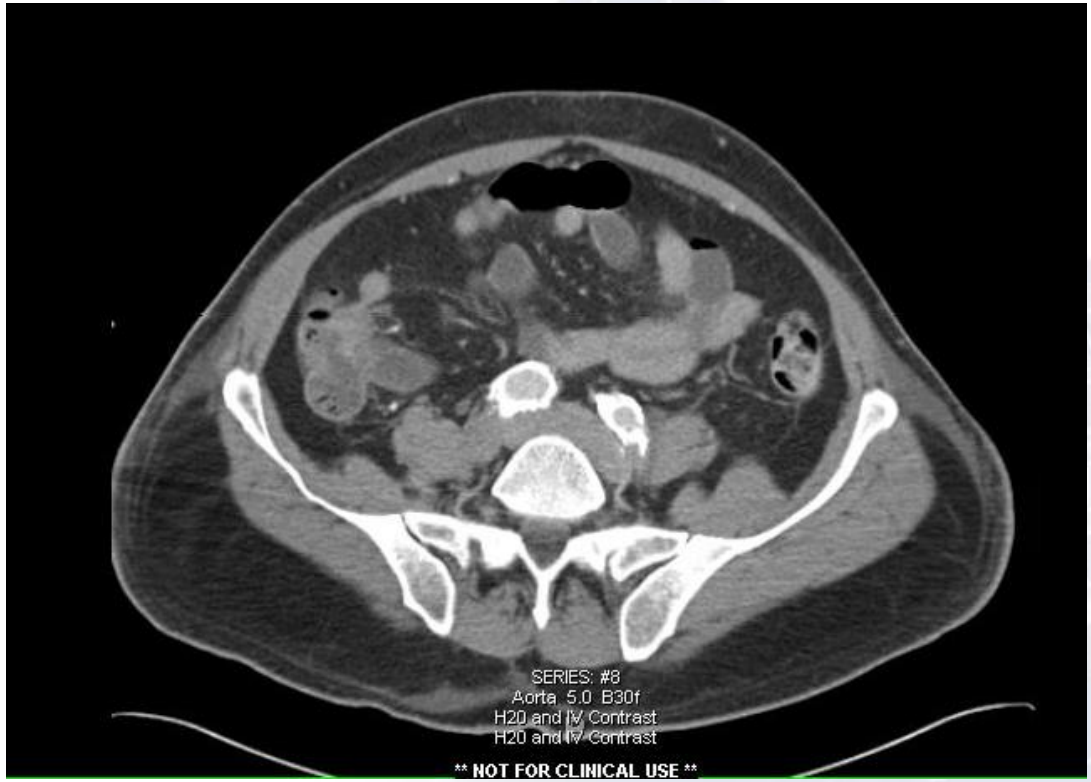
Heart of the matter. The aorta (arrows) of a normal mouse (A) and a losartan-treated mouse with a fibrillin-1 mutation (D) are indistinguishable, but those of mutant mice treated with a beta blocker (B) or placebo (C) have aneurysms.

Adh[erence] in recent litigation [appropriate]

JOHNS HOPKINS MEDICINE

The Modern Problem: Aging of the Aorta in MFS



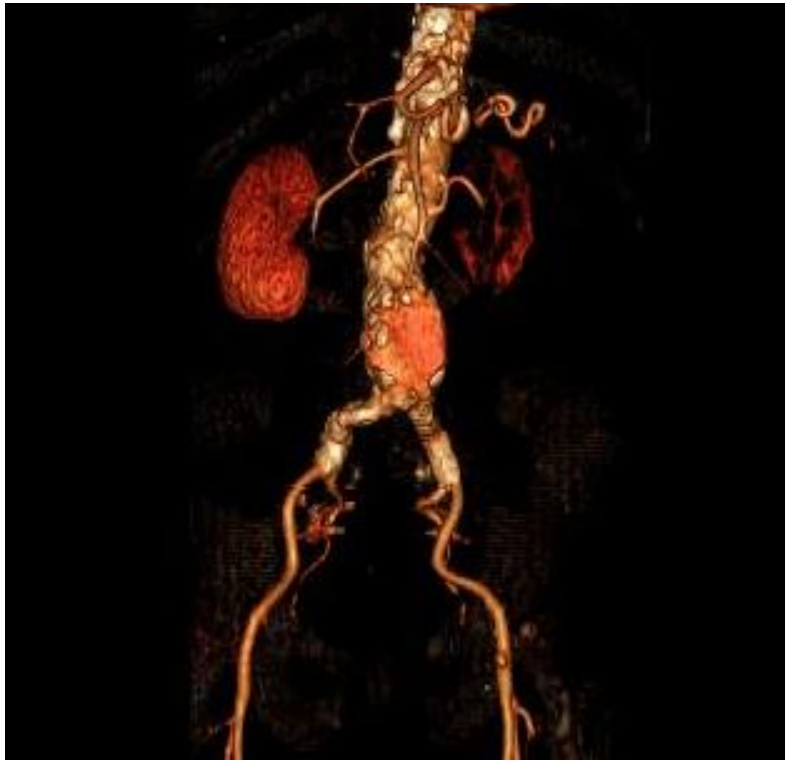


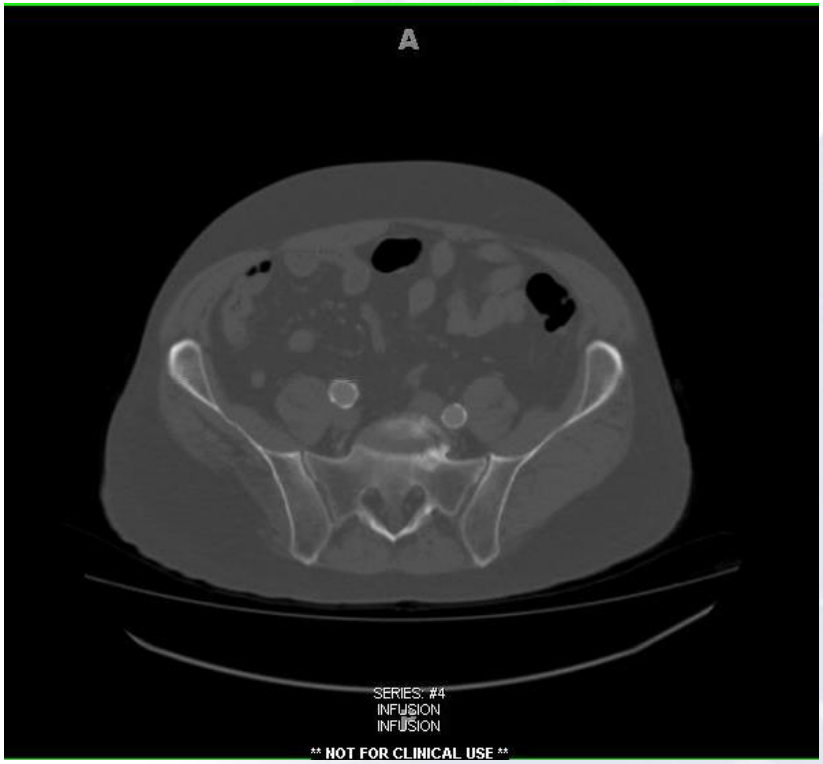
- 60 yo MFS, 17 yrs post CVG, nonsmoker

JOHNS HOPKINS MEDICINE

Aging of the Aorta in MFS

- 52 yo MFS, 15 yrs post CVG, 5yrs post TAAA, nonsmoker

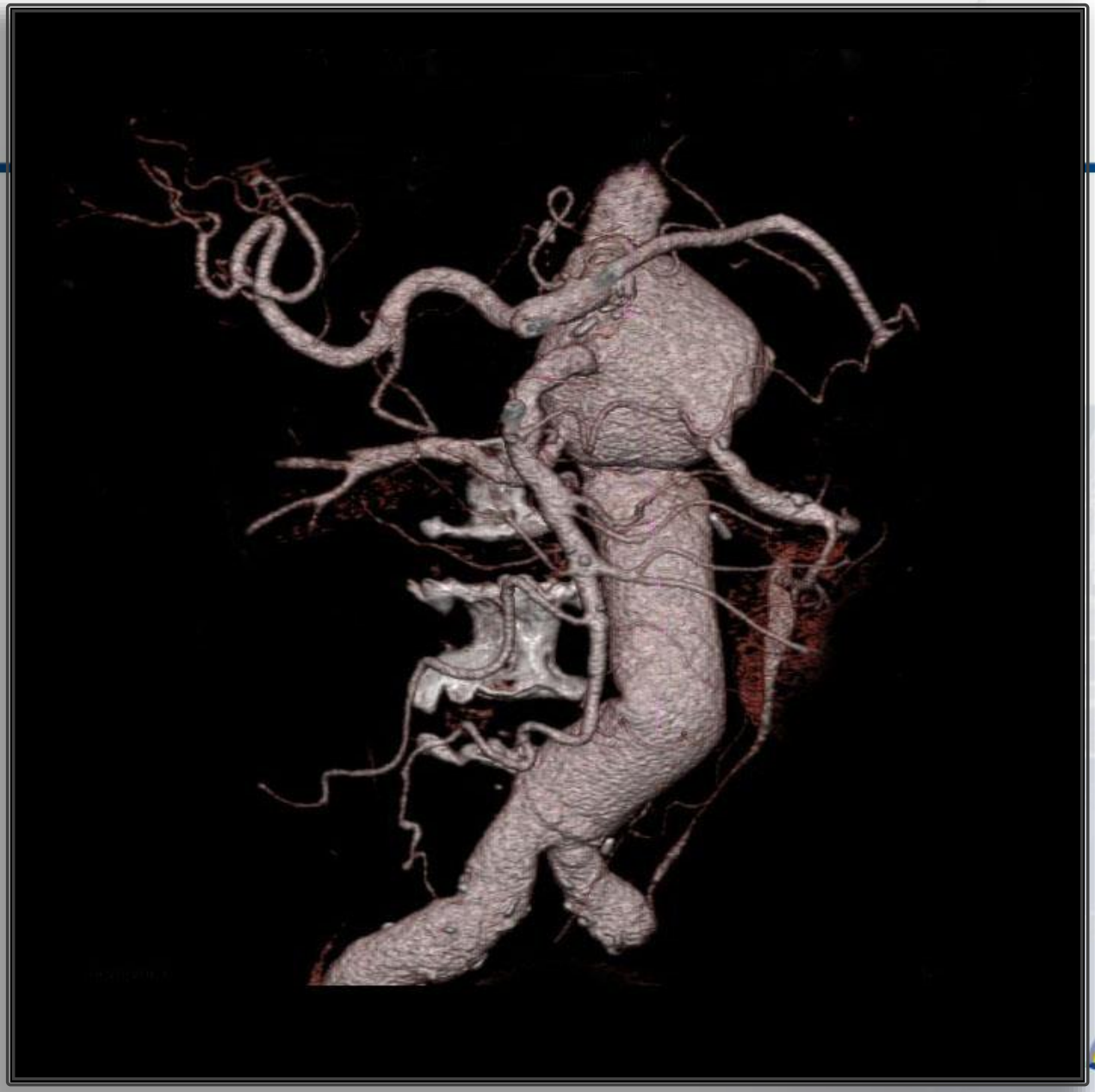




How should we handle these aging CTD patients?

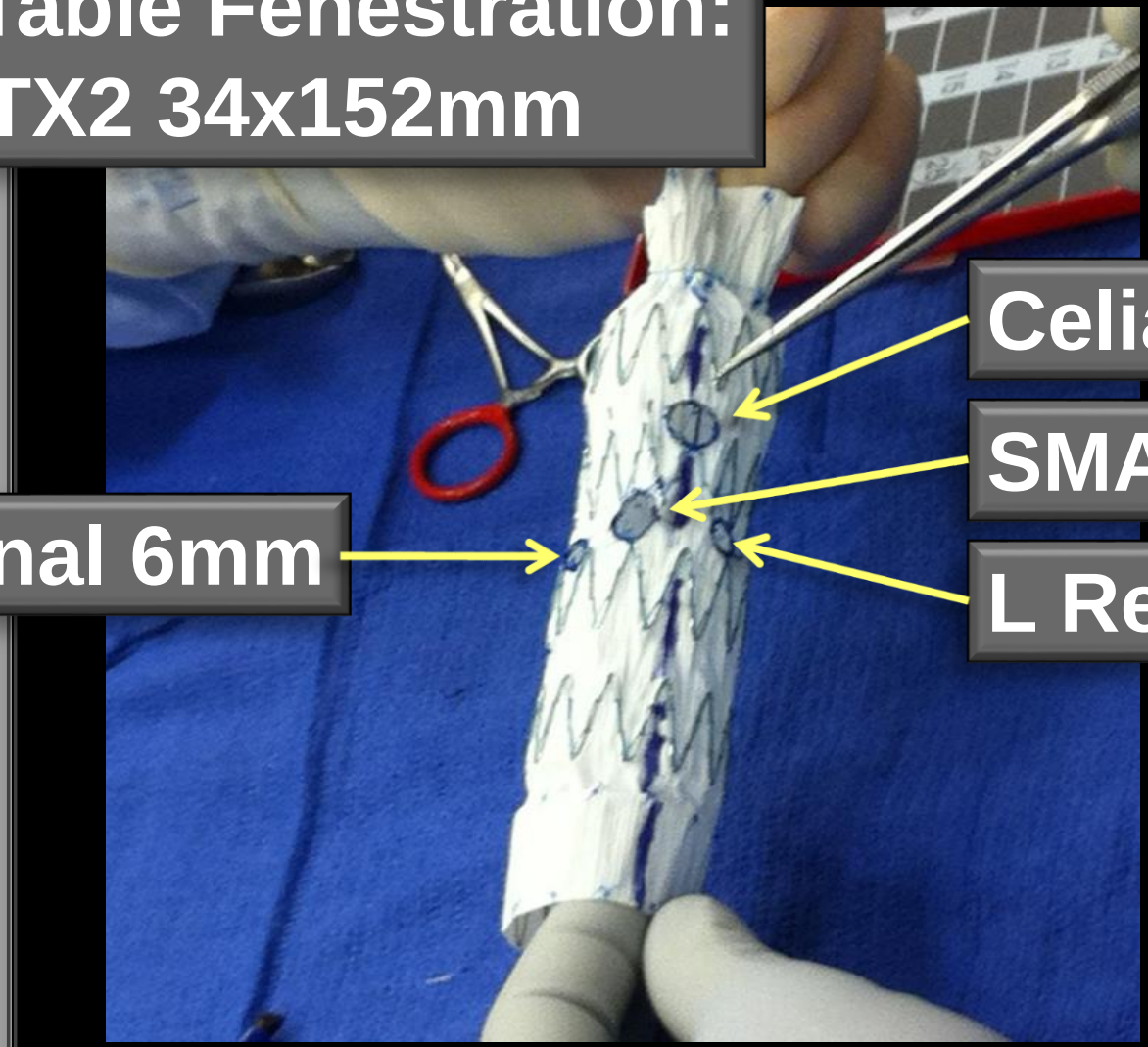
JOHNS HOPKINS MEDICINE

Pre-Procedure



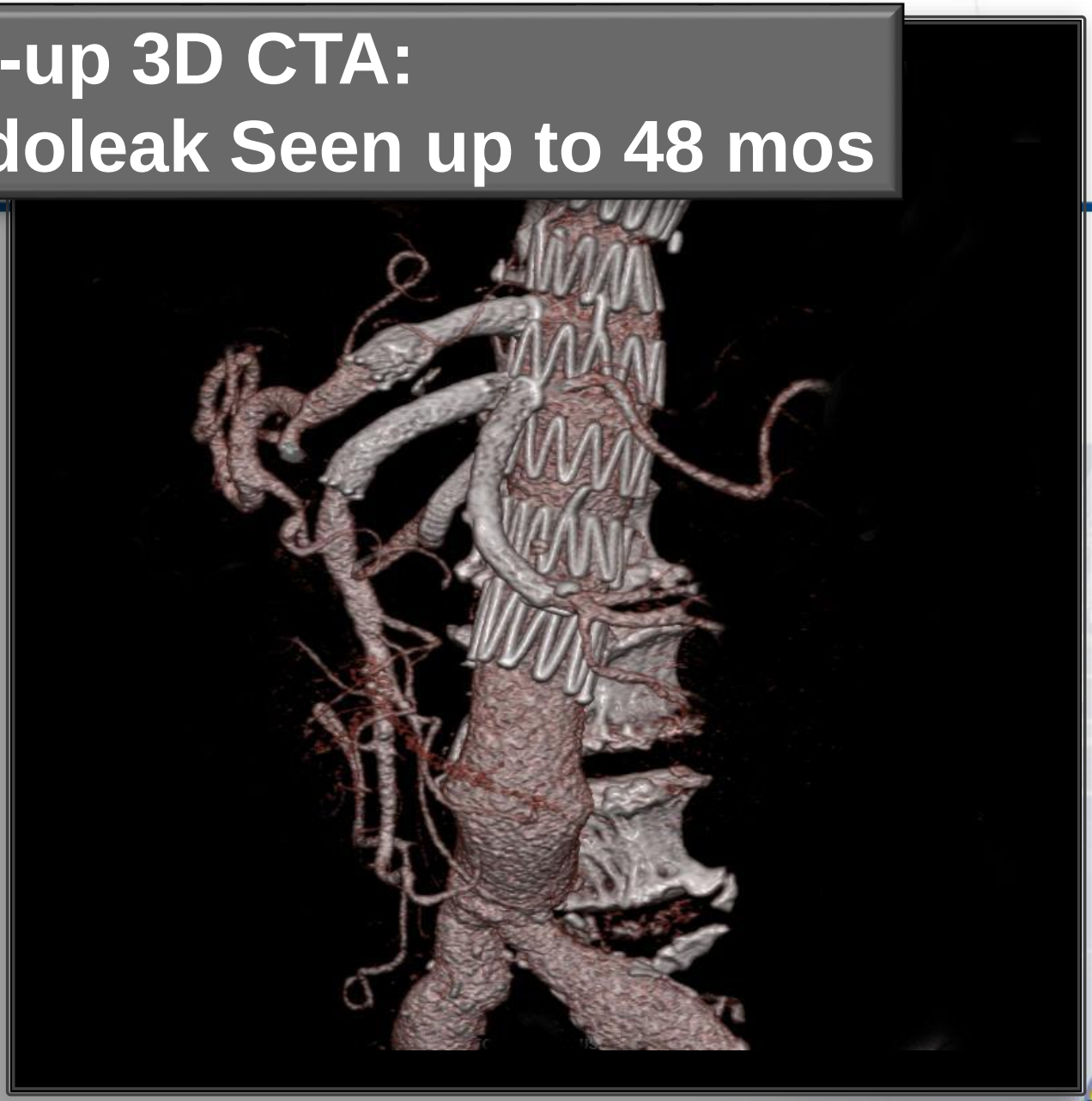
JOHNS HOPKINS
MEDICINE

Back Table Fenestration: Cook TX2 34x152mm



JOHNS HOPKINS MEDICINE

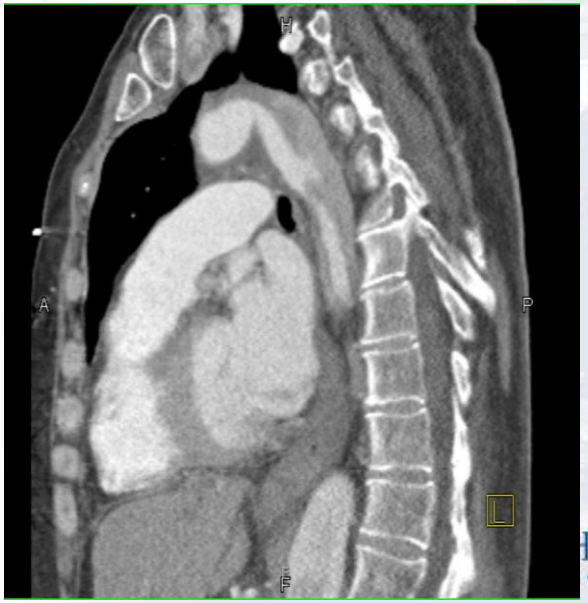
Follow-up 3D CTA:
No Endoleak Seen up to 48 mos



JOHNS HOPKINS
MEDICINE

Type B dissection in MFS

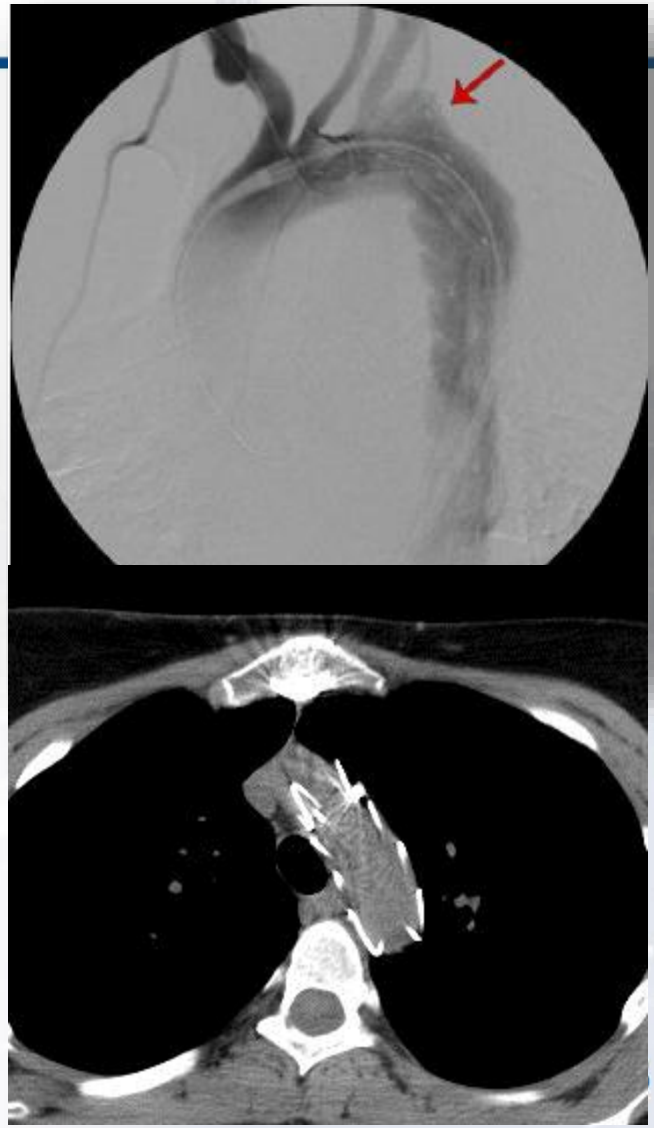
- Biologic basis for Type B dissection has been postulated.(Development, 2000)
  - -VSMCs from cardiac neural crest
- Time onset for Type B dissection after root aneurysm surgery is 14 yrs.
- DTA intervention after Type A dissection is 2.5 yrs.
- 50% pts will require DTA surgery over a mean of 26yrs.(JTCVS, 2009)



Concerns about TEVAR in MFS

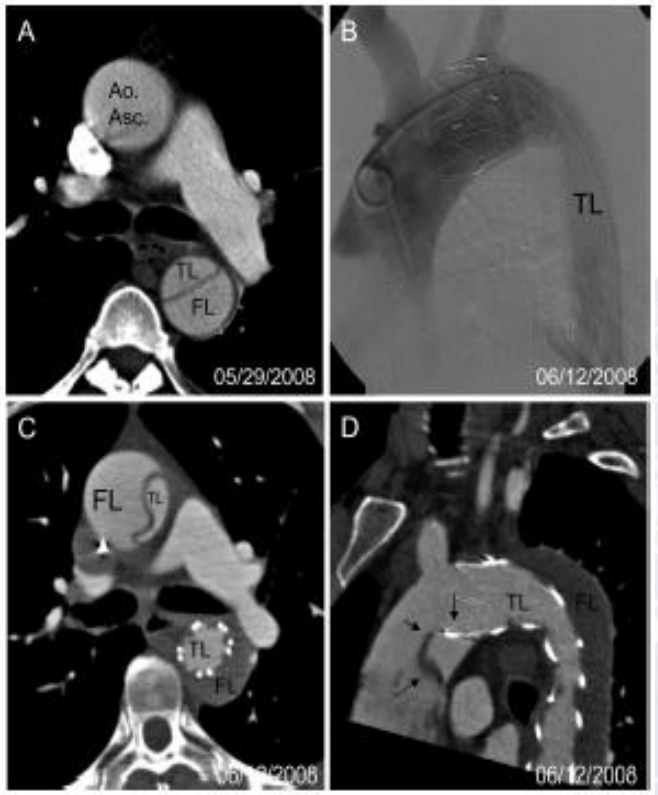
- 1. CTD exclusion of all devices to date
  - Device radial force.
  - Tendency of devices to straighten.
  - Bare metal stents?

- 2. Fragility of the aortic wall
  - Stent graft induced trauma.
  - Retrograde dissection.
  - Failure to control aorta remote to stent.



Retrograde Dissections in MFS

- The arch and ascending are at risk for rAAD. (Dong, Circulation, 2009)
  - Distal ascending and proximal arch are usually guidewire related.
  - Whole arch dissection is usually stent-graft induced (80%+).
- MFS pts accounted for 12% of rAAD cases, but were only 1% of series.
- "*Retrograde aortic dissection was the most common complication for MFS.*"



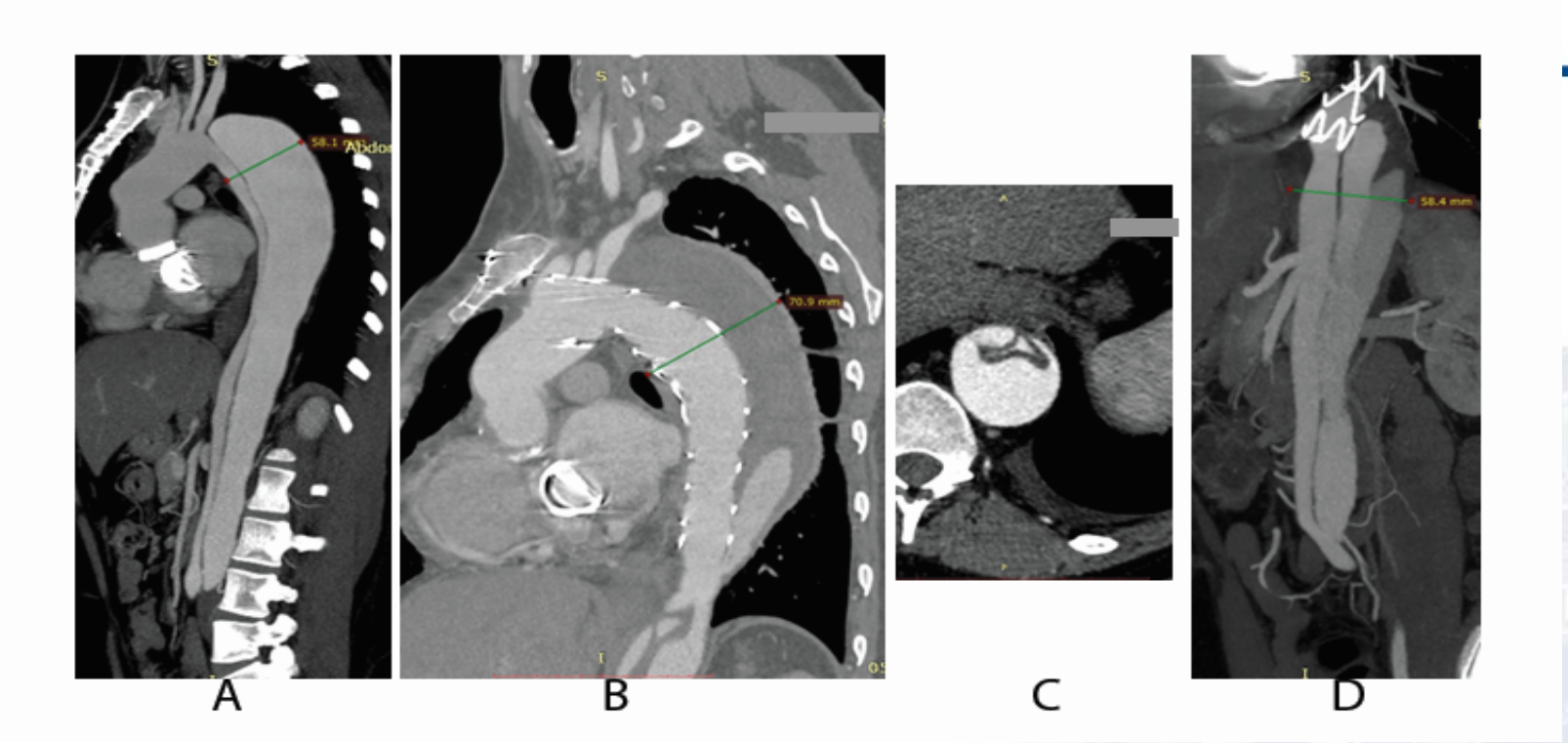
JOHNS HOPKINS MEDICINE

Where does TEVAR leave open TAAA Surgery in Marfan Syndrome?

- Evidence suggests TEVAR may be safe in short term, but device issues are central in local aortic complications, especially in acute Type B.
- There is potential benefit of TEVAR to stabilize acute DTA emergencies:
  - "Bridge" to definitive therapy in rupture
  - Allow referral to center where open TAAA surgery has matured excellent results.
  - STS/AATS Consensus, 2012

JOHNS HOPKINS MEDICINE

MFS TEVAR: *Bridge to definitive surgery*

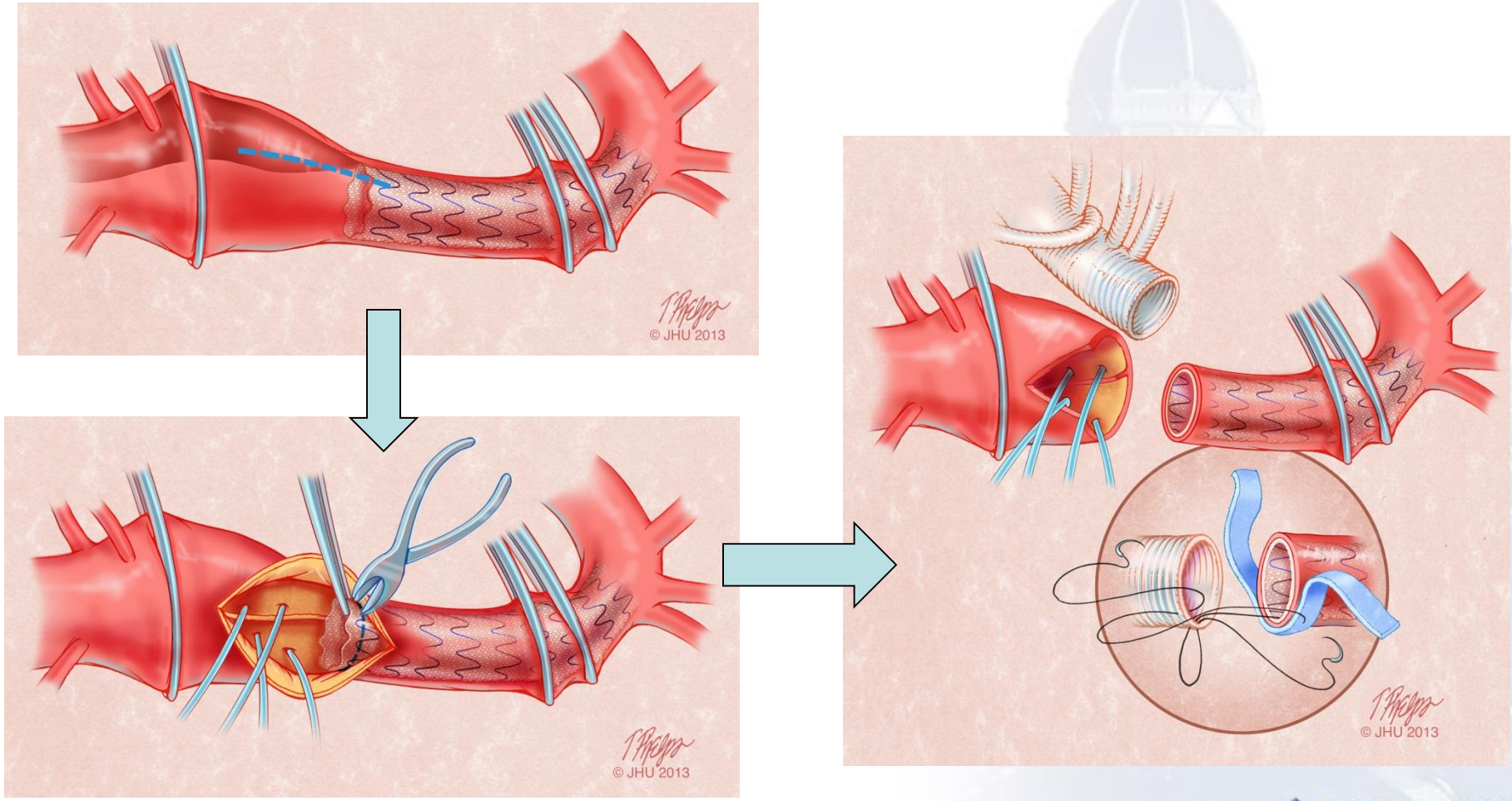


1wk	1mo	6mo	Referred
TEVAR	*New SINE*	*New AD*	*TAAA*

- Allowed referral to our center where open TAAA surgery has matured excellent results.

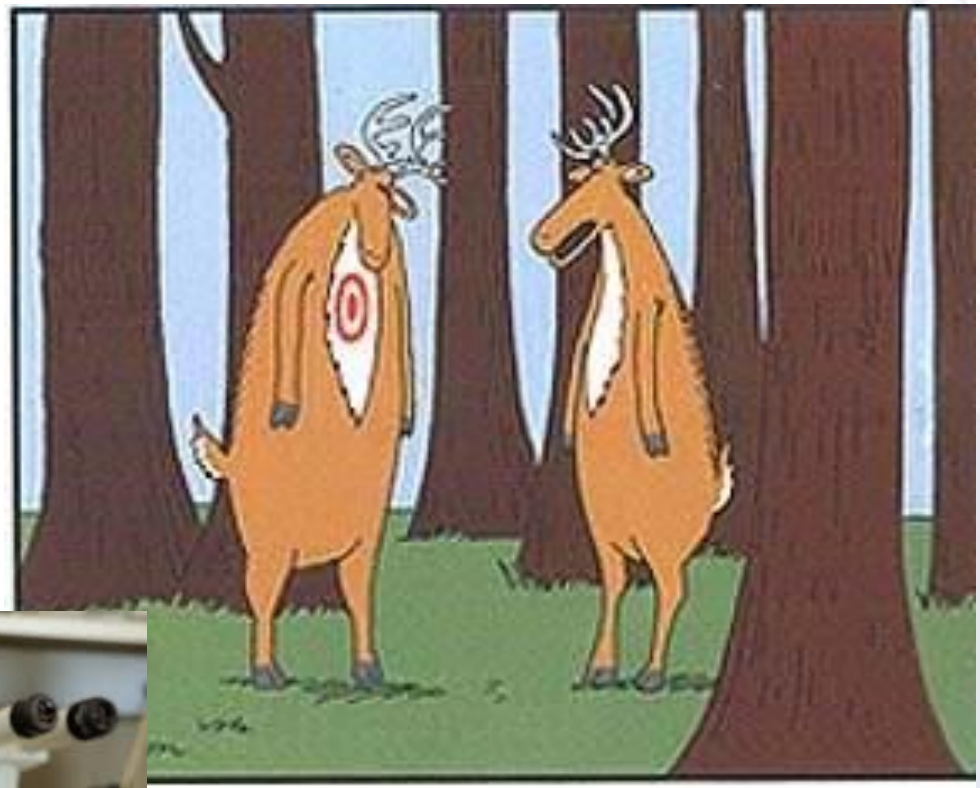
JOHNS HOPKINS MEDICINE

Conversion technique after TEVAR for TAAA.



JOHNS HOPKINS MEDICINE

- On call at JHH…Acute Dissection, VEDS

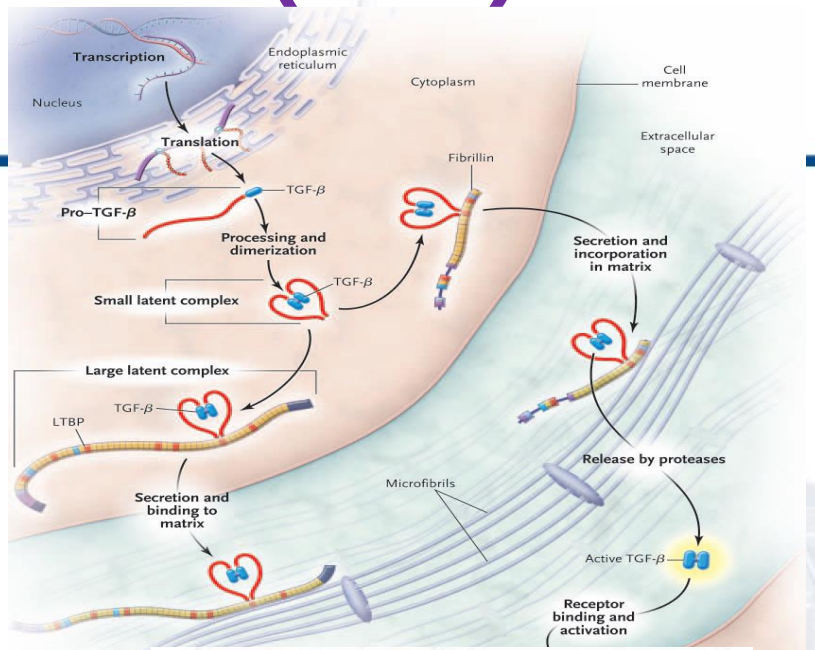


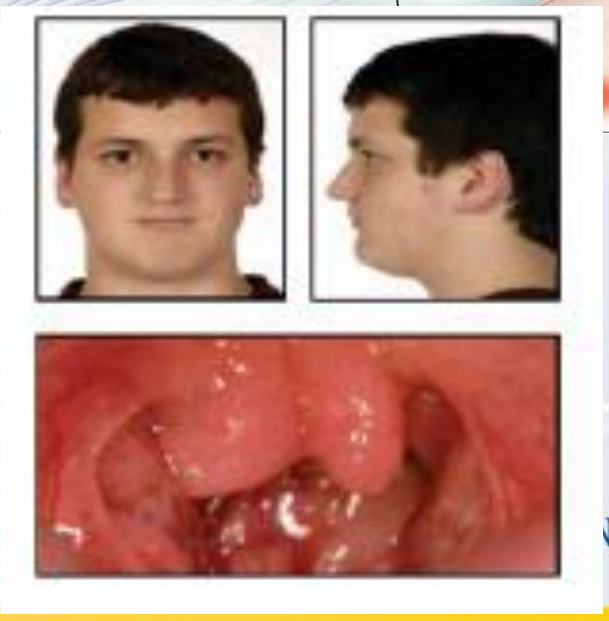
"Bummer of a birthmark, Hal."

JOHNS HOPKINS MEDICINE

Loeys-Dietz Syndrome (LDS)

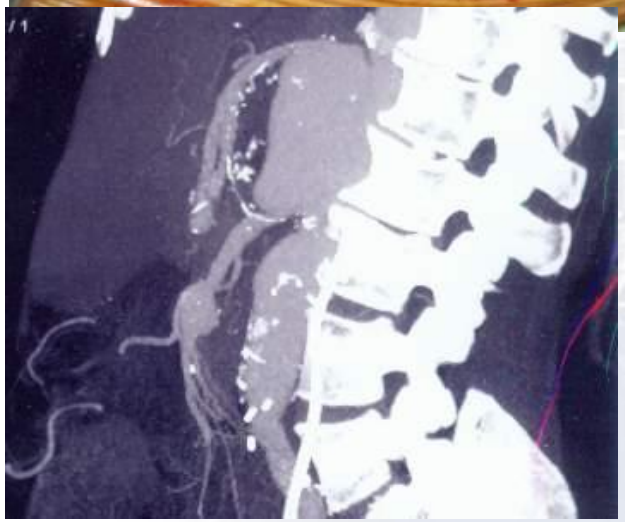
- Heterozygous mutations in TGFβR1 & TGFβR2 (NEJM, 2005)
- Characteristic triad:
  - Arterial tortuousity and aneurysm
  - Hypertelorism
  - Craniofacial (cleft palate, bifid uvula)
- LDS Type I
  - First CV 16.9 & death 22.6 yrs
- LDS Type 2
  - First CV 26.9 & death 31.8 yrs
- LDS 3 (SMAD3), LDS 4(OA&AAA)





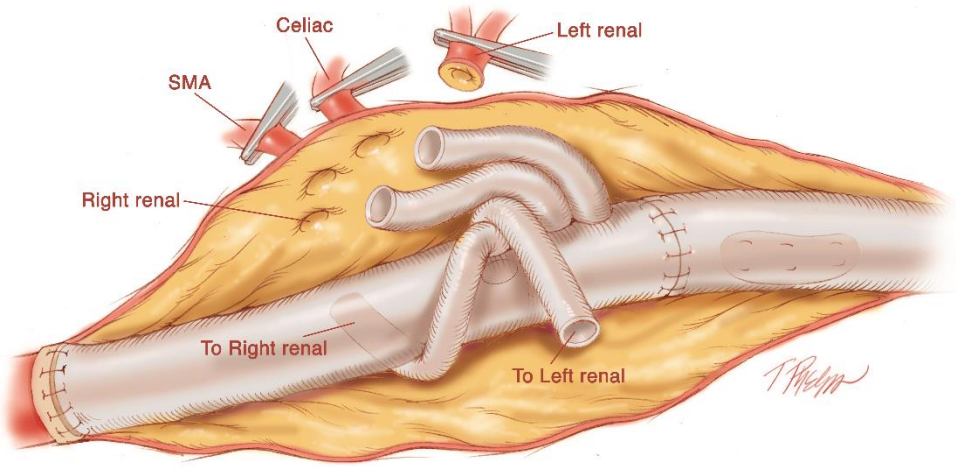
Loeys-Dietz: *Pan-Aortopathy*

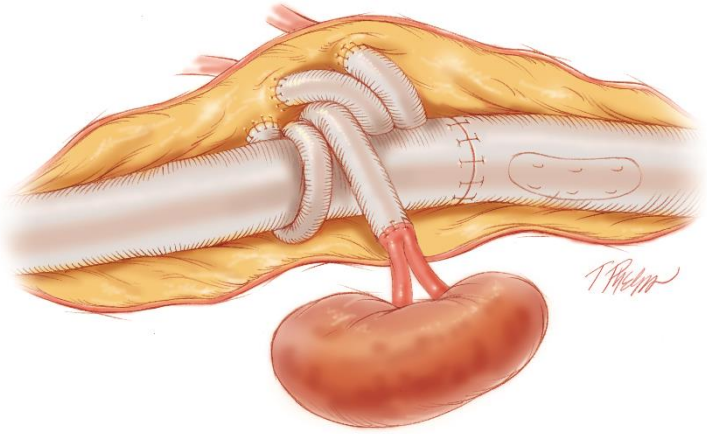
- Degeneration of contiguous aorta or inclusion patches
- JHH series of 107 pts, JVS 2001
  - 17 CTD
  - 6/17 (35%) returned with patch aneurysm vs 5.6% atherosclerotic aneurysm pts
  - Mean time to dx 6.5 yrs
  - Rapid recurrence – LDS!

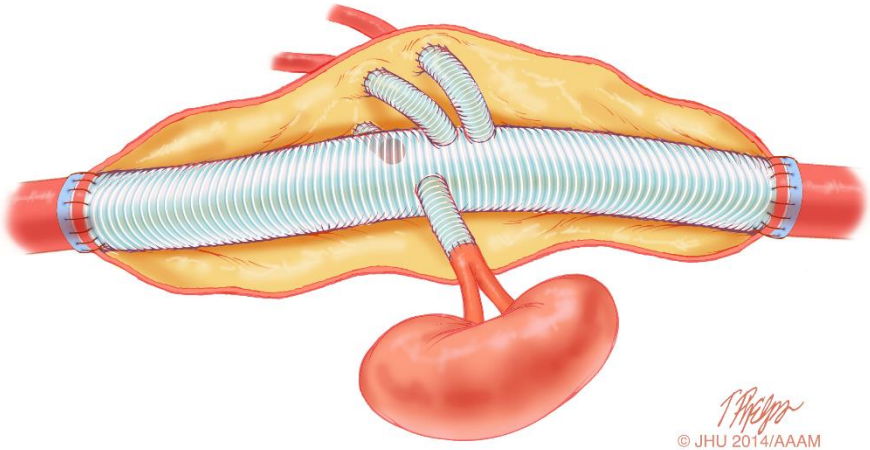


JOHNS HOPKINS MEDICINE

Technical Notes: Graft Configurations







JOHNS HOPKINS MEDICINE

Results: Perioperative Outcomes

(Hi

POD 4 Arch rupture (non-contiguous)
POD 7 Cerebral hemorrhage
POD 46 Chylothorax/sepsis

Characteristic	CTD (N=29)	Degenerative (N=108)	p-value
In-hospital mortality	10.3% (3)	5.6% (6)	0.40
Acute branched graft thrombosis	0.0% (0)	6.5% (7)	0.16
Perioperative complication*	62.1% (18)	54.6% (59)	0.47
Acute kidney injury	17.2% (5)	19.4% (21)	0.79
Hemodialysis	6.9% (2)	13.9% (15)	0.53
Pneumonia	10.3% (3)	11.1% (12)	1.0
Urinary tract infection	10.3% (3)	9.3% (10)	1.0
Respiratory failure	10.3% (3)	7.4% (8)	0.70
Bowel ischemia	0% (0)	8.3% (9)	0.11
Stroke	6.9% (2)	2.8% (3)	0.29
VTE	3.5% (1)	3.7% (4)	1.0
Bleeding	0% (0)	3.7% (4)	0.58
Lower extremity ischemia	3.5% (1)	2.8% (3)	1.00
Spinal headache	6.9% (2)	1.9% (2)	0.20
Heart failure	0% (0)	3.7% (4)	0.58
Myocardial infarction	0% (0)	2.8% (3)	1.0
Surgical site infection	3.5% (1)	1.9% (2)	0.51
Atrial fibrillation	3.5% (1)	0.9% (1)	0.38
Paraplegia	3.5% (1)	0.9% (1)	0.38

JOHNS HOPKINS MEDICINE

Results: Midterm Outcomes

77% left renal artery bypass

Characteristic	C[illegible]	[illegible]	p-value
Follow-up [months (median IQR)]	[illegible]	[illegible]	1.00
Overall mortality	10.3% (3)	13.9% (15)	0.76
Loss of branched graft patency	0% (0)	7.8% (13)	0.04
New aortic dissection	3.5% (1)	2.8% (3)	1.0
New aneurysm (total)	24.1% (7)	8.3% (9)	0.02
Aortic	20.7% (6)	6.5% (7)	0.02
Visceral	0% (0)	0% (0)	--
Iliac/peripheral	13.8% (3)	3.7% (4)	0.04
Contiguous with repair	66.7% (6)	63.6% (7)	0.66
Creatinine (most recent; mg/dL)	1.4±0.3	1.4±0.1	0.22

JOHNS HOPKINS MEDICINE

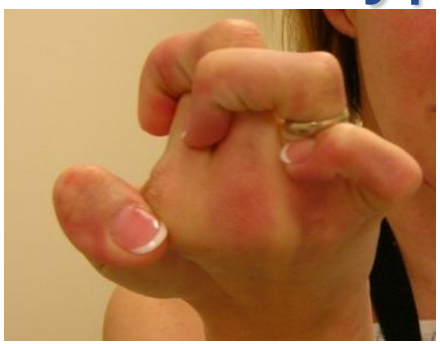
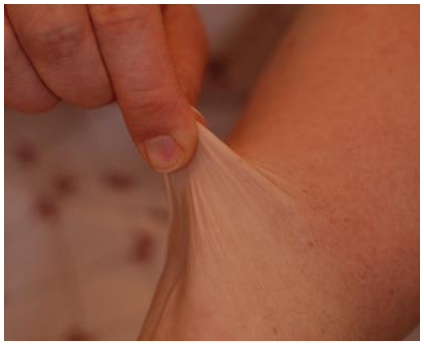
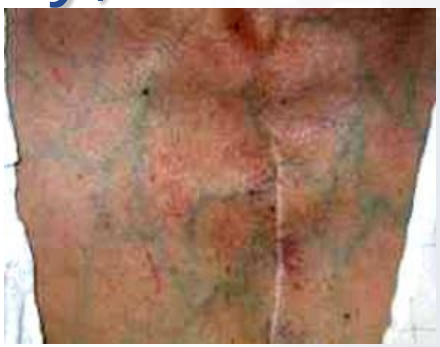
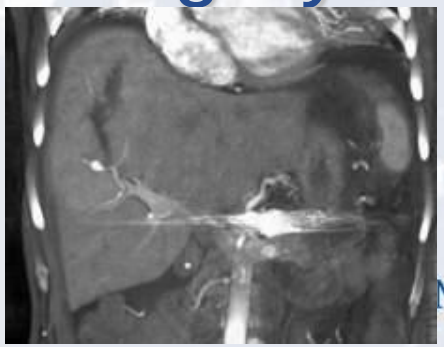
Loeys-Dietz Key Points

- Loeys-Dietz Syndrome is an aggressive pan-aortic aneurysm syndrome.
- Proper recognition is clinically possible with bedside physical examination.
- ***Identification of LDS may expedite prophylactic surgery (versus VEDS, as both young).***
- Initial operative experience is encouraging, but recurrent aneurysm is common, both contiguous and non-contiguous. (Ann Vasc, 2016, JVS 2017)

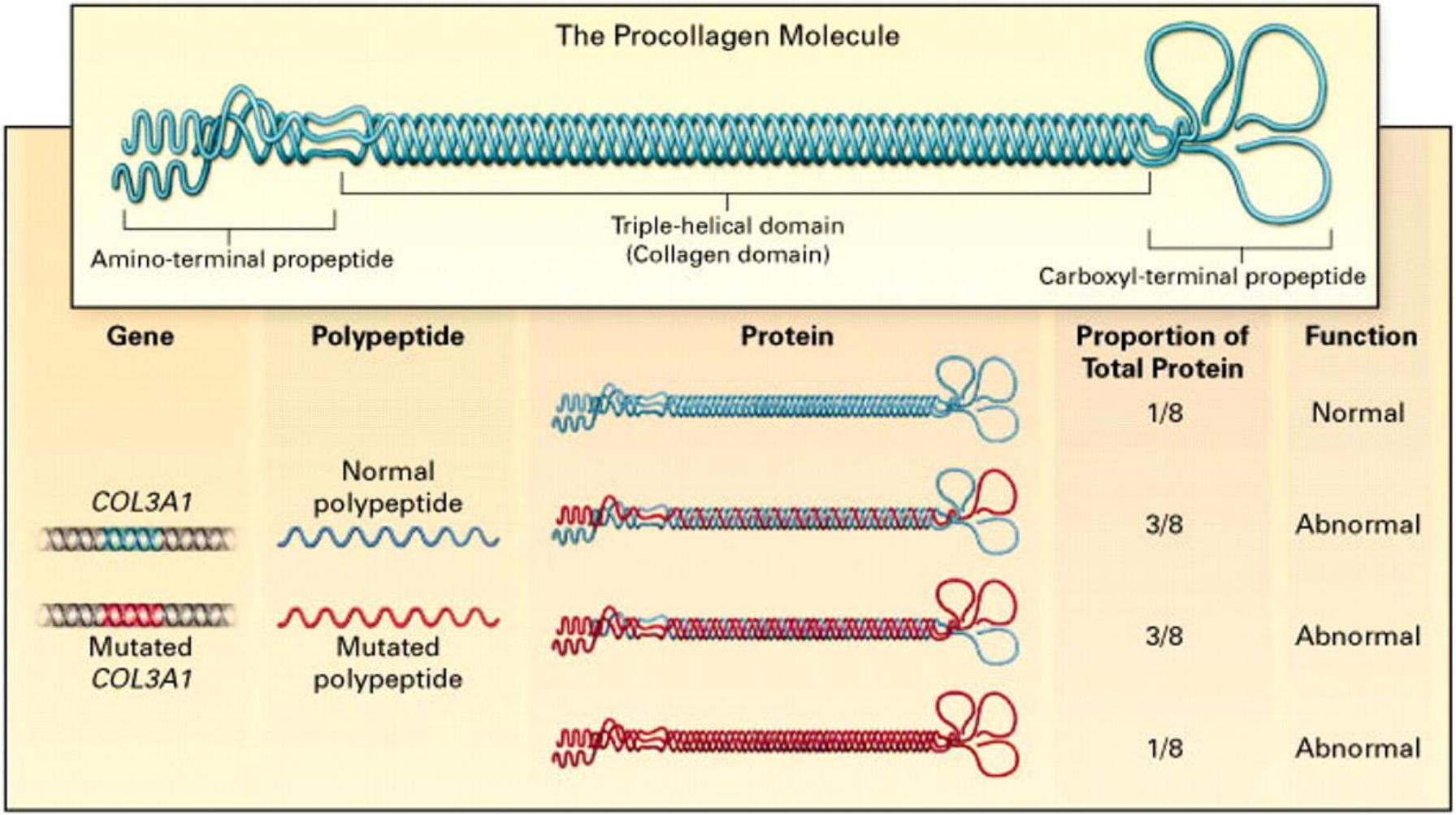
JOHNS HOPKINS MEDICINE

Ehlers-Danlos Syndrome (EDS)

- Hereditary Connective Tissue Disorder
  - Mutations in genes regulating collagen matrix
- Six Different EDS Subtypes
  - Classical, Hypermobility, Vascular, Kyphoscoliotic, Arthrochalasic, & Dermatosparactic.
- Characterized by Joint Hypermobility, Skin Hyperextensibility, & Tissue Fragility

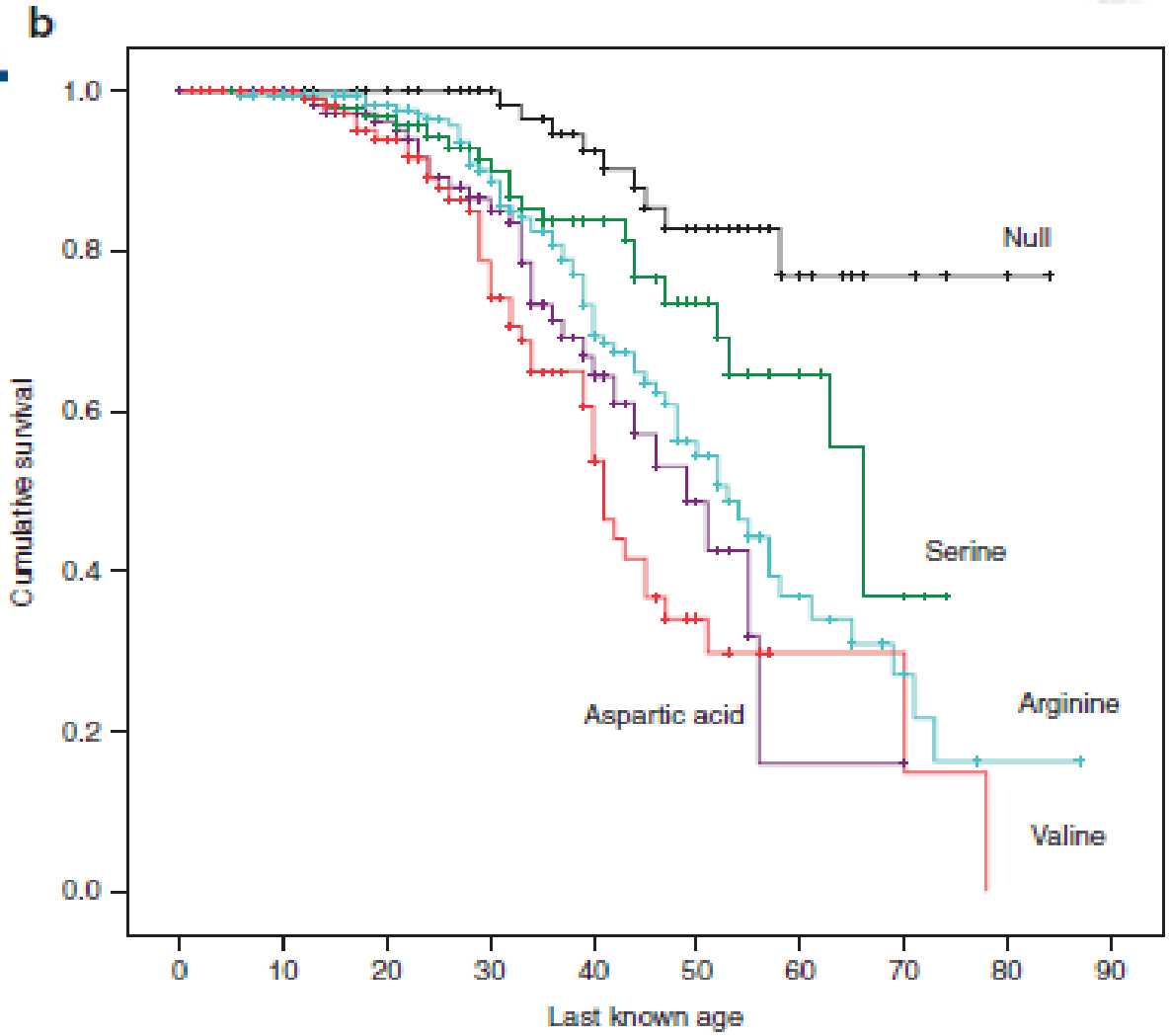
Collagen structure



From NEJM **Pyeritz 342 (10): 2000**

JOHNS HOPKINS MEDICINE

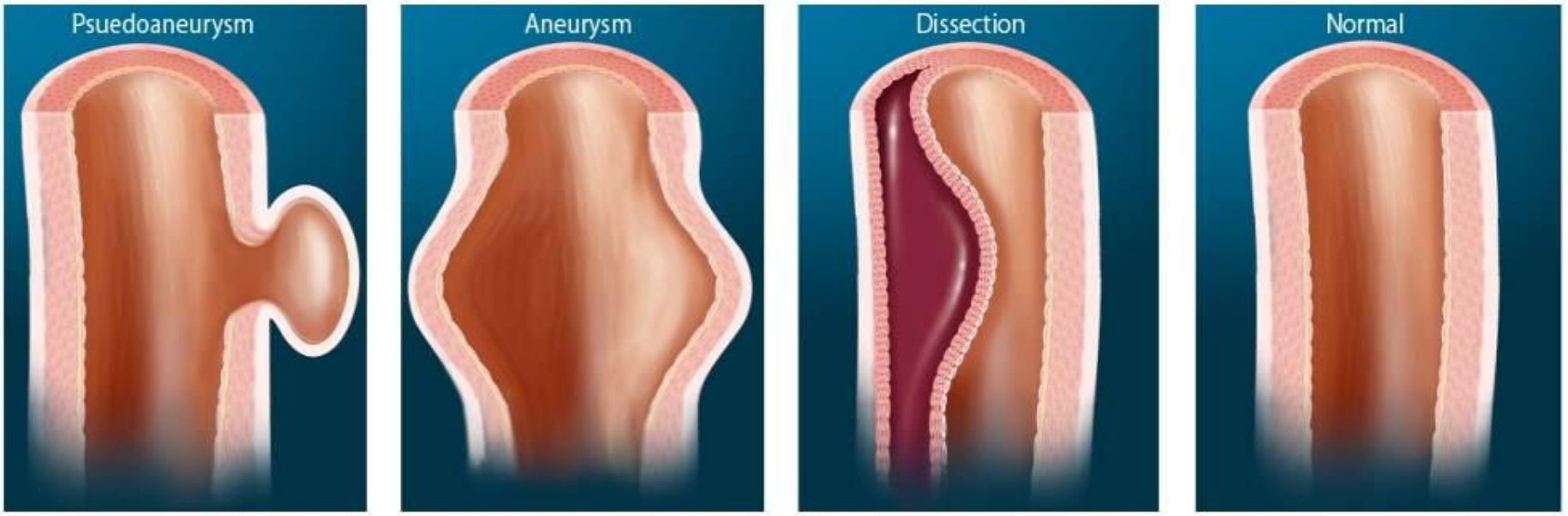
Collagen structure



Pepin, Genet in Medicine, 2014

JOHNS HOPKINS MEDICINE

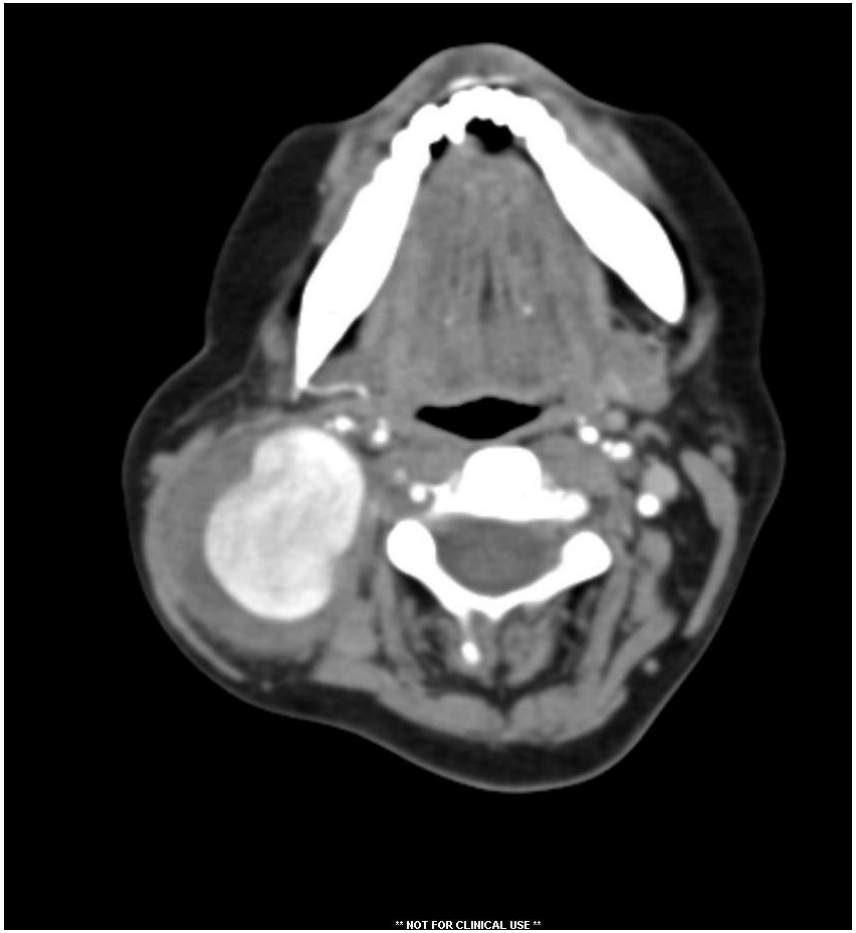
Truth, Lies, and Statistics…..

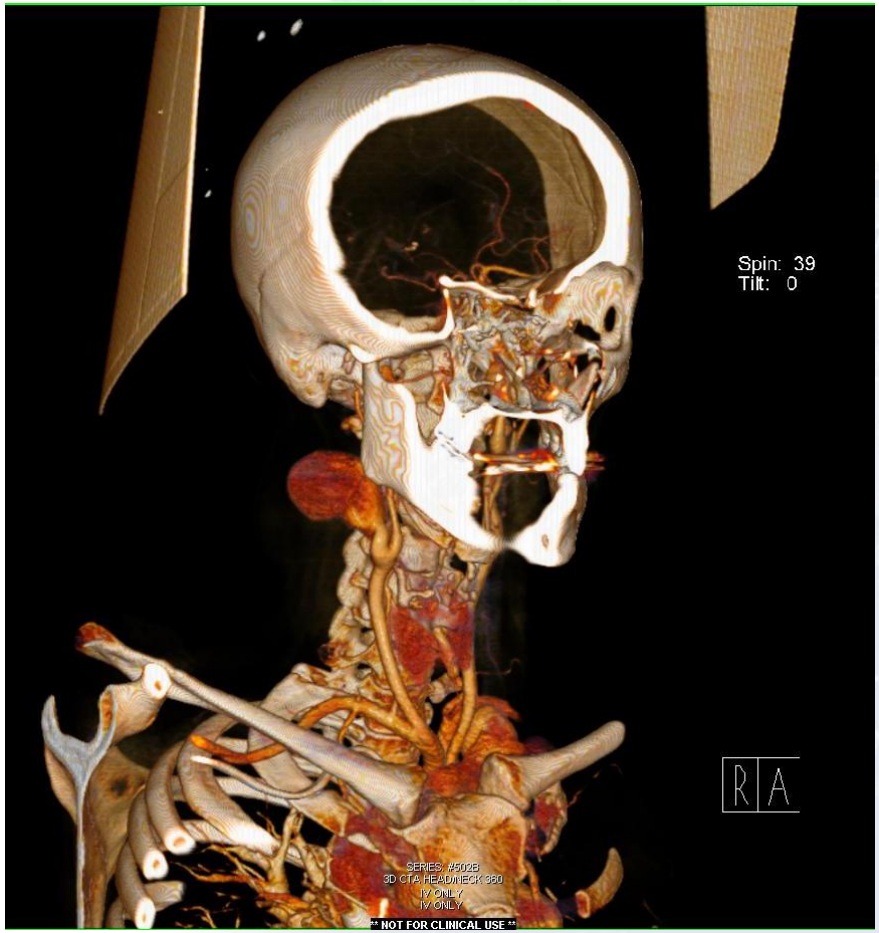


– Most common arterial pathology is pseudoaneurysm, and these are often Asx

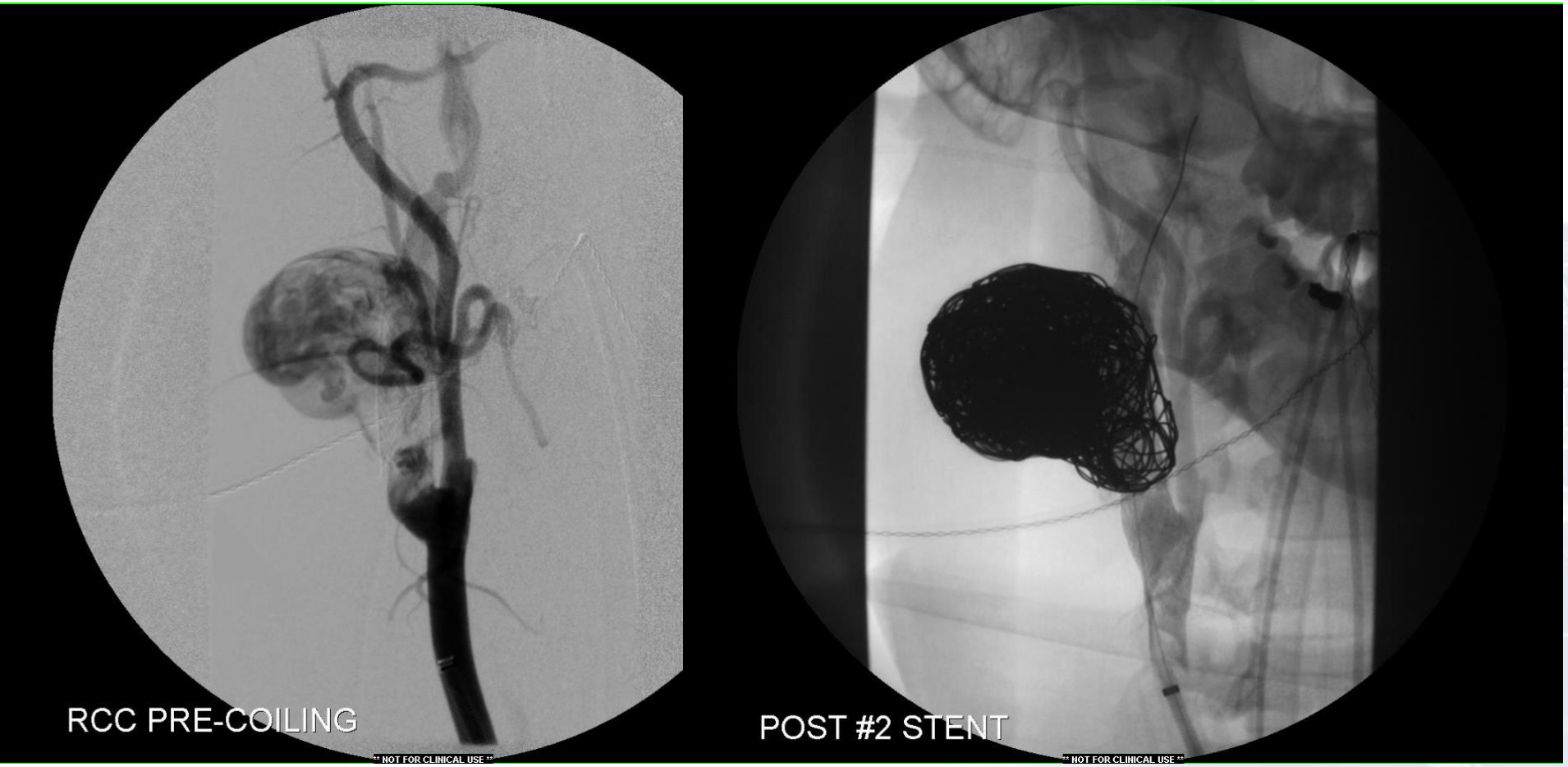
Endovascular frontier…..

- Think creatively…





Endovascular frontier…..



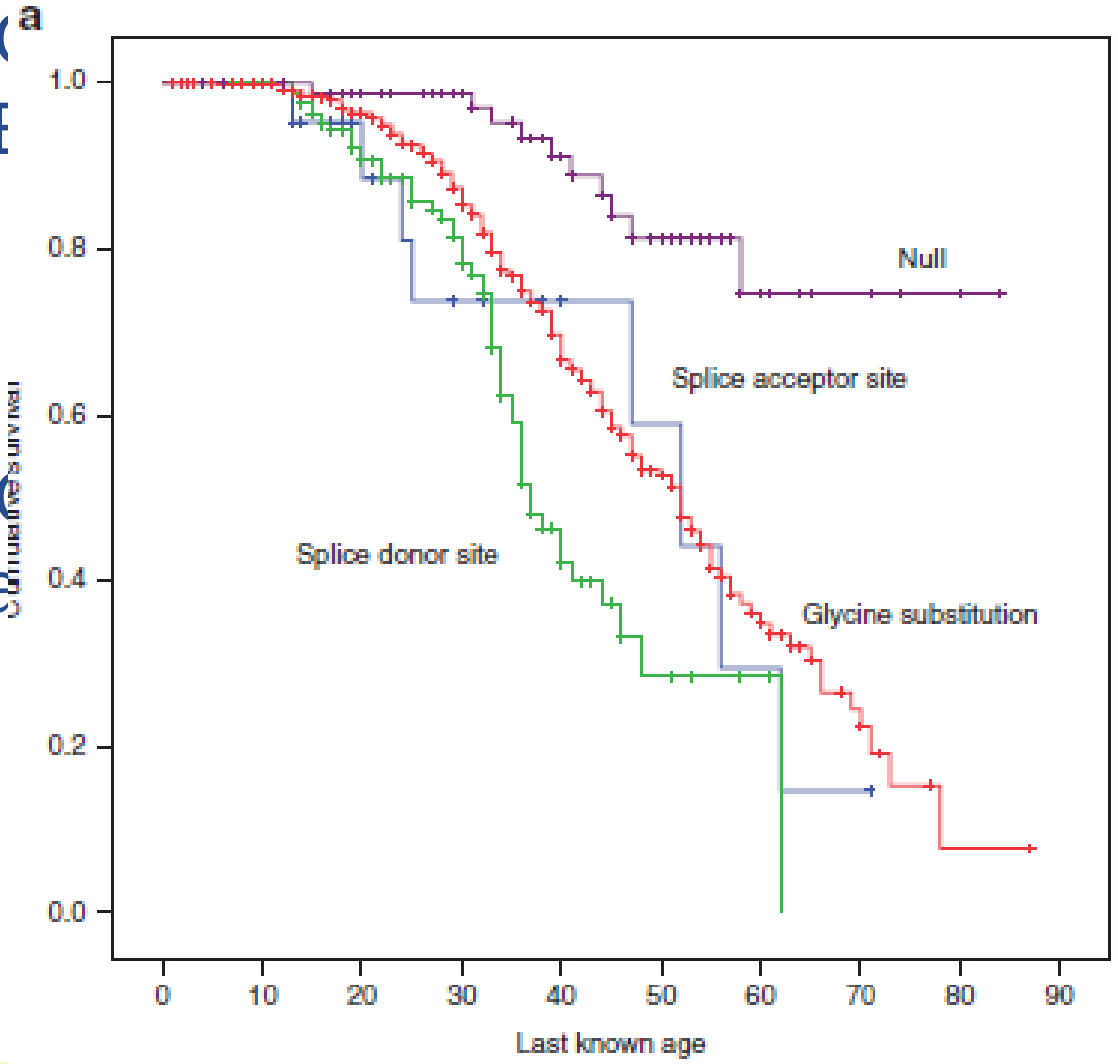
JOHNS HOPKINS MEDICINE

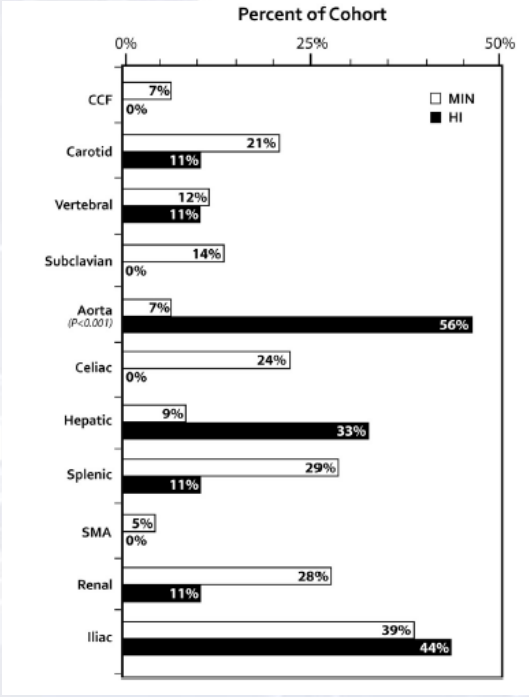
Selection of VEDS Patients for Therapy:

influence of specific genotypes (Shalub, JVS, 2014)

- C(
  VE
  - –
  - –
- C(
  ha
  - –
  - –

ng

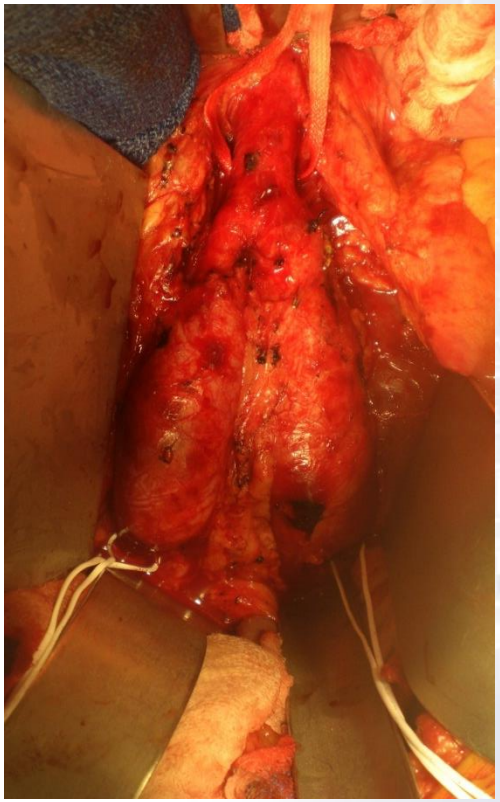


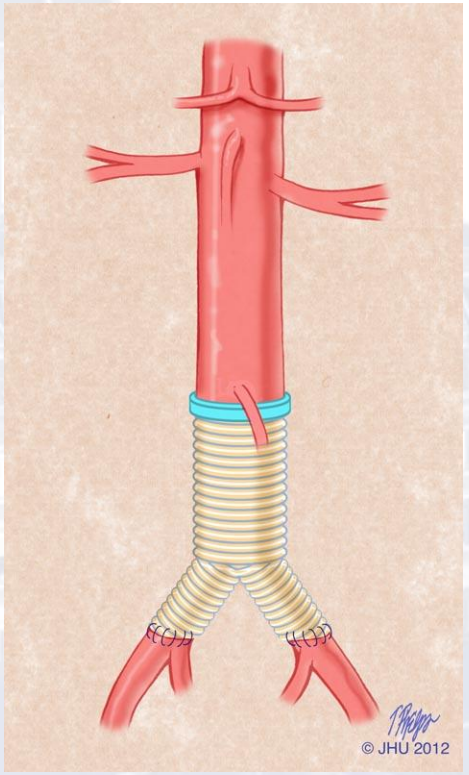


JOHNS HOPKINS MEDICINE

Open Surgery Considerations in VEDS

- Careful intubation
- Sonosite© for lines
- Strict BP control
- Induced hypotension
  - SBP <90 mmHg
- No Rommels on vessels
- Never reclamp same vessel location.
  - *"Fall-back position"*





JOHNS HOPKINS MEDICINE

In-Hospital Outcomes

Endovascular Procedures (N=49)

Outcome	Classic EDS (n=15)	Hypermobile EDS (n=27)	Vascular EDS (n=7)	P-Value
Operative Death – no (%)	0 (0)	0 (0)	0 (0)	NS
In-Hospital Death – no (%)	0 (0)	0 (0)	0 (0)	NS
LOS – median (IQR)	1 (1-2)	2 (1-2)	3 (1-6)	0.51
Any Complication – no (%)	0 (0)	1 (4)	0 (0)	0.37

Open Procedures (N=22)

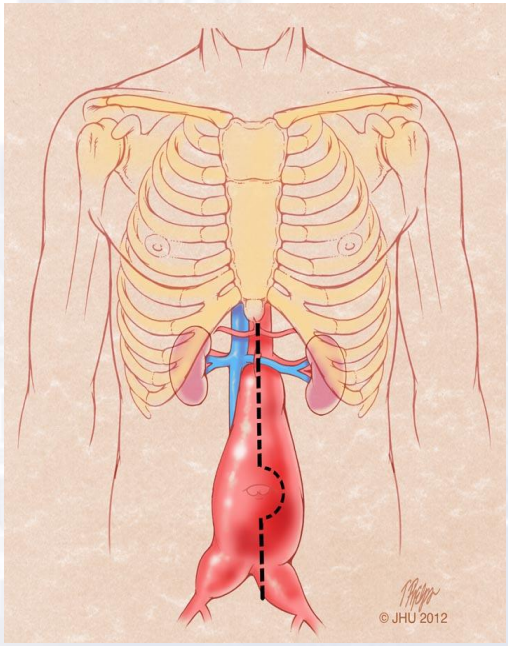
Outcome	Classic EDS (n=7)	Hypermobile EDS (n=4)	Vascular EDS n=11	P-Value
Operative Death – no (%)	0 (0)	0 (0)	1 (10)	0.61
In-Hospital Death – no (%)	0 (0)	0 (0)	1 (10)	0.56
LOS – median (IQR)	7 (5-8)	5 (2-8)	7 (6-12)	0.86
Any Complication – no (%)	3 (29)	0 (0)	3 (30)	0.58

VEDS Conclusions

- Prompt diagnosis is key (versus LDS) and reproductive counseling is encouraged.
- Our results suggest the majority of VEDS pts with vascular disease can, *and should be*, managed electively with minimal morbidity & mortality.
- Prior recommendations to defer vascular interventions in VEDS pts until urgent or emergent presentation may not be warranted with contemporary management.

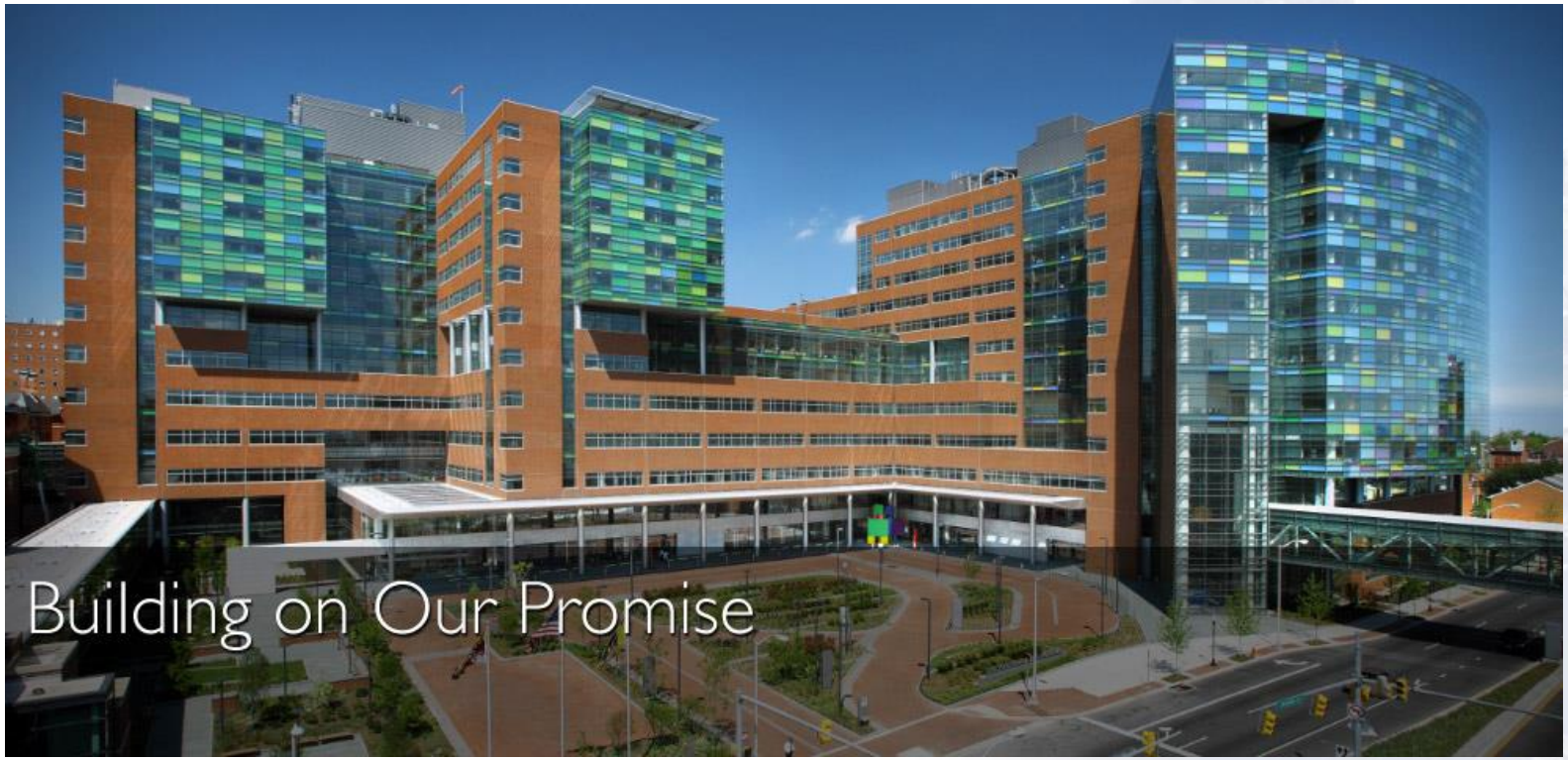
Contemporary CTD Management

- Multidisciplinary evaluation by geneticist, anesthesiologist, and surgeon.
- Liberal use of techniques to reduce operative trauma.
- Stent-graft therapy in CTD is defined in limited fashion.
  - Graft-to-graft sealing zones.
  - Revision procedures
  - Reoperative exposures
  - “Bridge” to referral



JOHNS HOPKINS MEDICINE

Thank you



JOHNS HOPKINS MEDICINE