

Genotype-surgical phenotype: How this impacts surgical decision making



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Vascular Genetics Symposium

10/3/2025



Disclosures

Advisory boards

- The Ehlers-Danlos Society
- Marfan Foundation





Genotype-surgical phenotype: How this impacts surgical decision making

- Recognize the Spectrum of Genetic Aortopathy and Its Clinical Implications
- Diameter-Based Thresholds and Aortic Vulnerability: Understand how genotypic and phenotypic factors, tissue integrity, and vascular remodeling contribute to aortic rupture risk



Current clinical paradigms

Aortic diameter (ascending or abdominal) is a marker for risk of dissection or rupture

Endovascular repair relies on sac exclusion and aortic remodeling

The aorta is
a Structural
Conduit

The aorta is
a dynamic,
living system



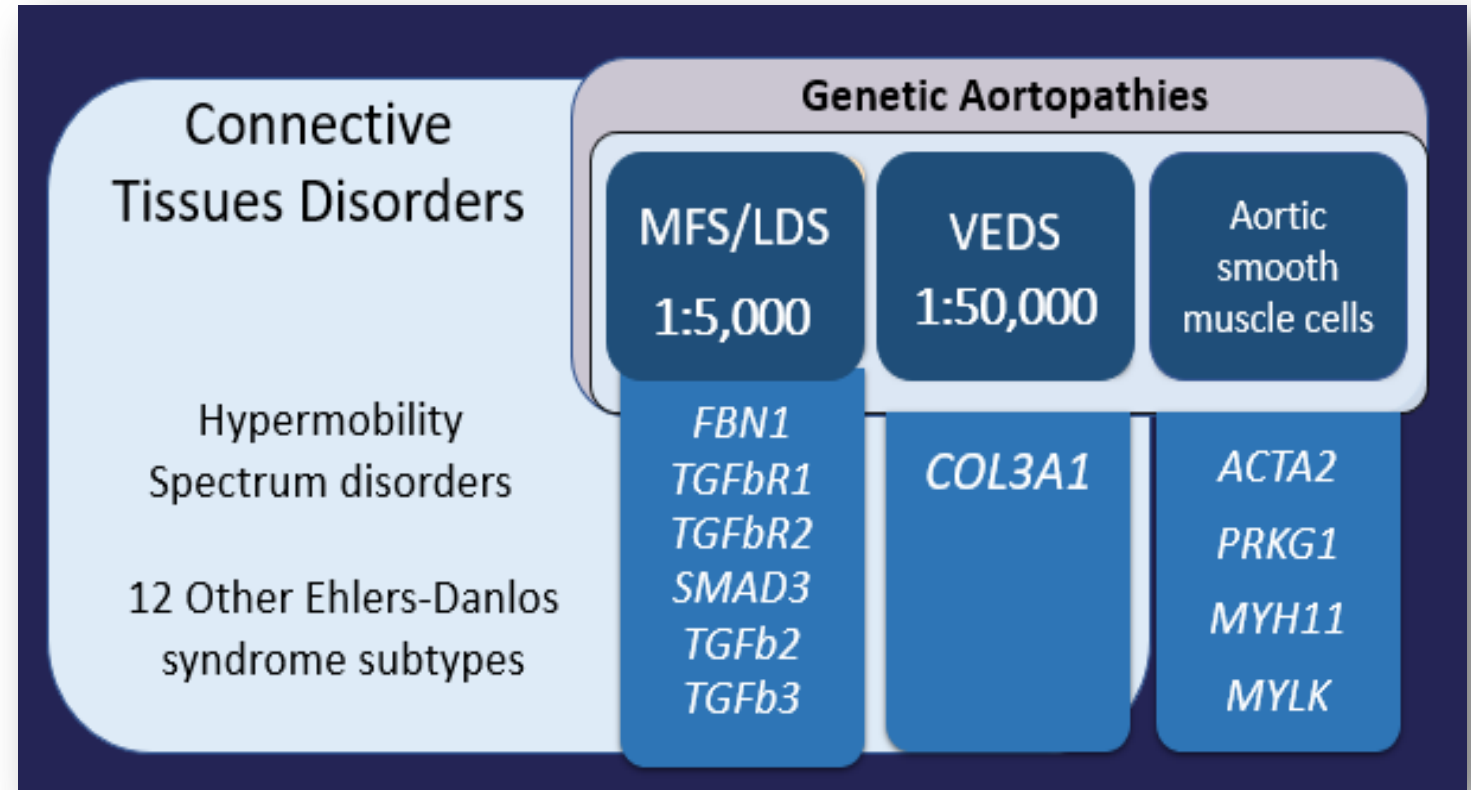
MIND THE GAP

The disconnect between anatomy and tissue biology
is at the heart of our most frustrating outcomes



Genetic Aortopathies

- Abnormal extracellular matrix components (Elastin, Fibrillin, Collagens)
- Altered TGF- β signaling
- Disrupted smooth muscle cell function



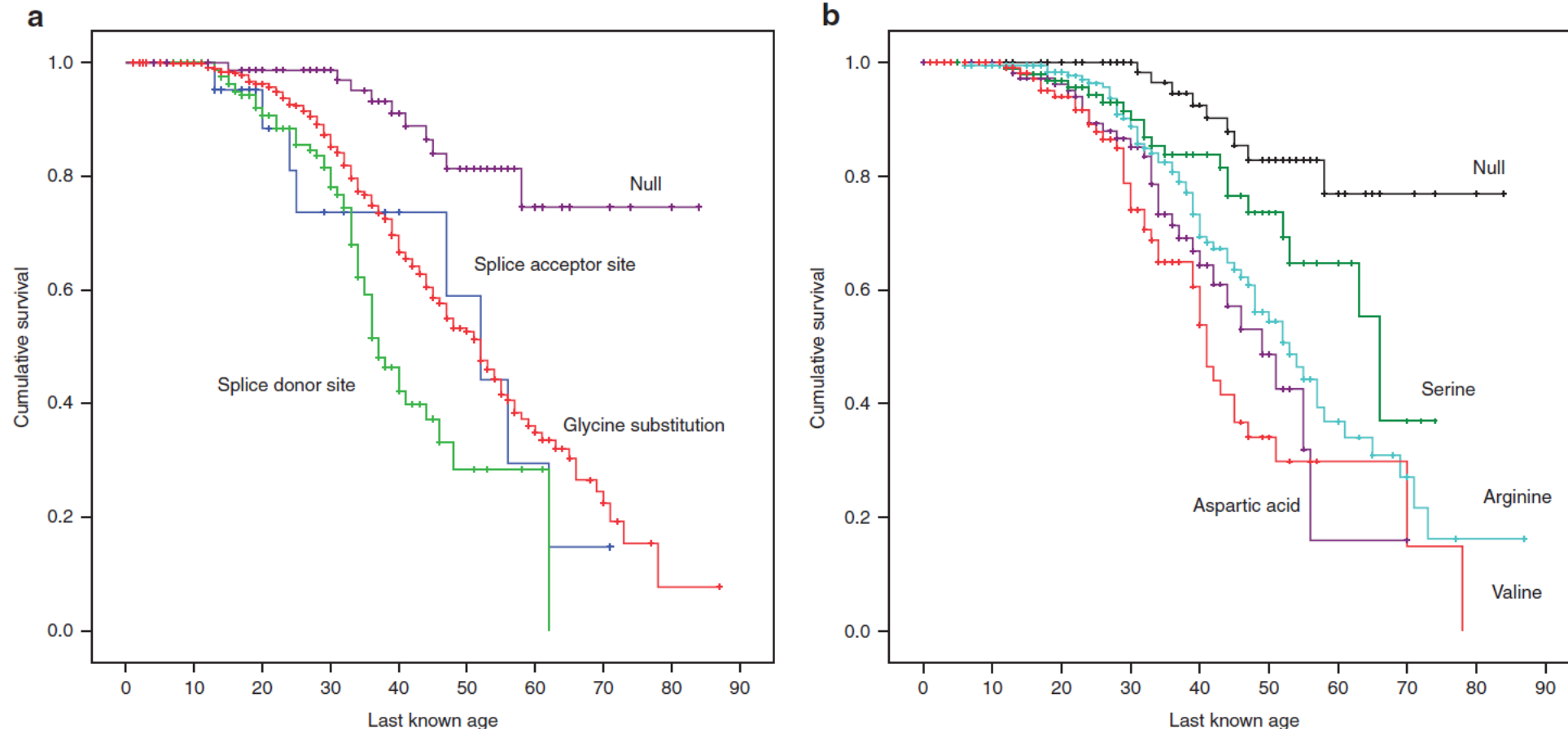
Premature aging of the aorta: Elastic fibers fragmentation, smooth muscle cells loss, proteoglycans accumulation



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

Melanie G. Pepin, MS¹, Ulrike Schwarze, MD¹, Kenneth M. Rice, PhD², Mingdong Liu, PhD²,
Dru Leistritz, MS¹ and Peter H. Byers, MD^{1,3}

GENETICS in MEDICINE | Volume 16 | Number 12 | December 2014

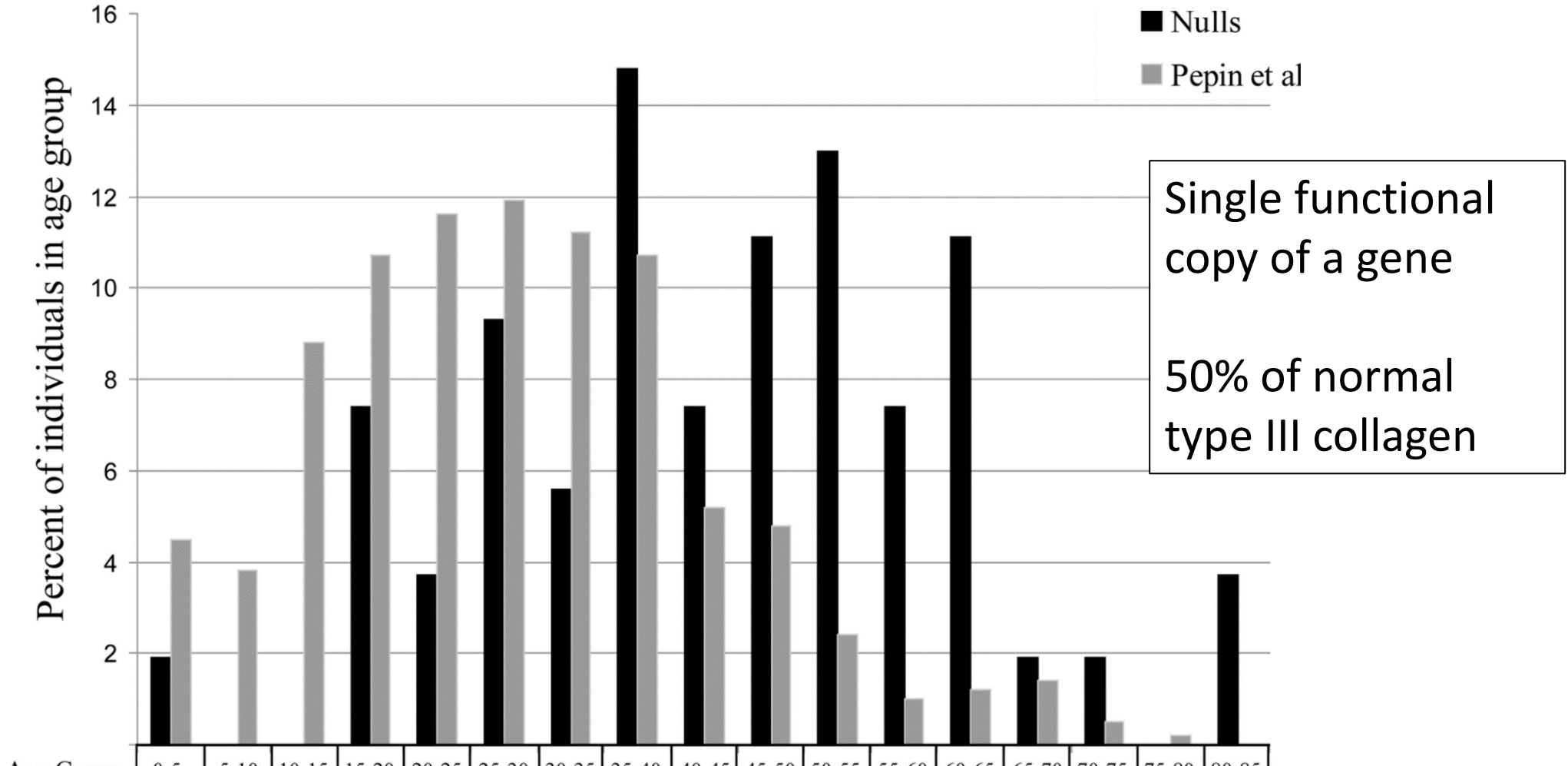




COL3A1 haploinsufficiency results in a variety of Ehlers-Danlos syndrome type IV with delayed onset of complications and longer life expectancy

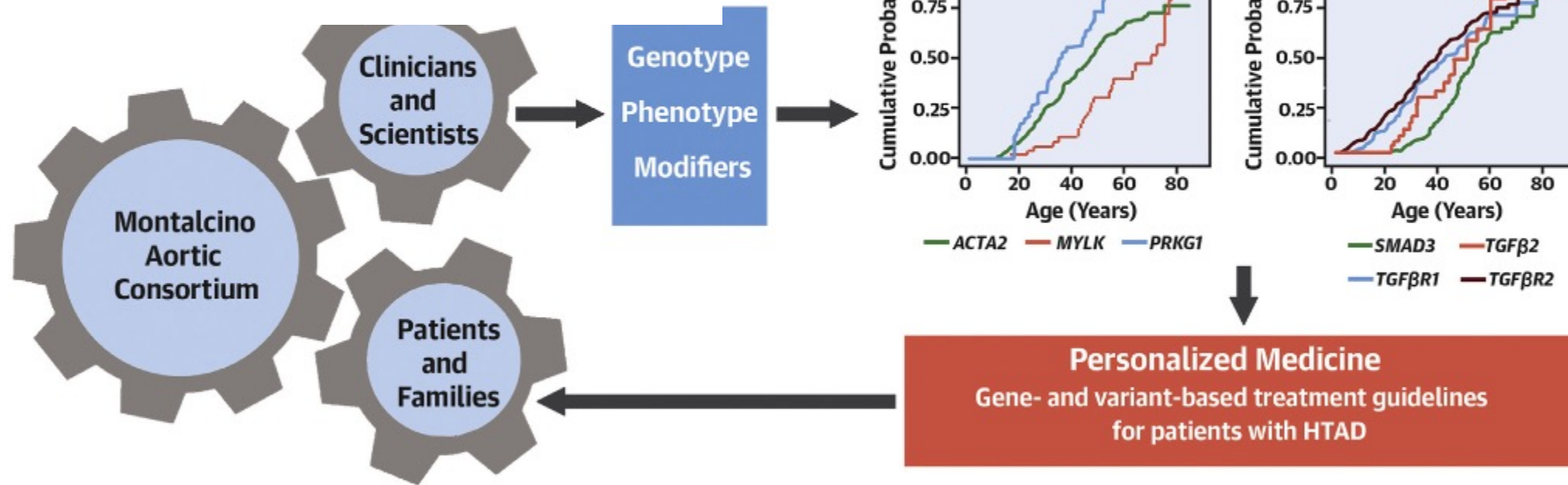
Dru F. Leistriz, MS¹, Melanie G. Pepin, MS¹, Ulrike Schwarze, MD¹, and Peter H. Byers, MD^{1,2}

Genetics IN Medicine • Volume 13, Number 8, August 2011



Comparative Risks of Initial Aortic Events Associated With Genetic Thoracic Aortic Disease

Ellen S. Regalado, PhD,^a Shaine A. Morris, MD, MPH,^b Alan C. Braverman, MD,^c Ellen M. Hostetler, BA,^a Julie De Backer, MD, PhD,^{d,e} Ruosha Li, PhD,^f Reed E. Pyritz, MD, PhD,^g Anji T. Yetman, MD,^h Elena Cervi, MD,ⁱ Sherene Shalhub, MD,^j Richmond Jeremy, MB, BS, PhD,^k Scott LeMaire, MD,^l Maral Ouzounian, MD, PhD,^m Arturo Evangelista, MD,^{e,n} Catherine Boileau, PhD,^{e,o} Guillaume Jondeau, MD, PhD,^{e,o} Dianna M. Milewicz, MD, PhD^a



Data were collected from probands and family members with rare variants in seven genes predisposing to heritable thoracic aortic disease. Using these data, risk and type of first aortic event were stratified based on both the altered gene and recurrent variants within the genes.

Characterization of Syndromic, Non-Syndromic Familial, and Sporadic Type B Aortic Dissection (TBAD)



Retrospective single-center review



389 patients with TBAD

HERITABLE TBAD



Syndromic TBAD

- Marfan syndrome
- Loeys-Dietz syndrome
- Vascular Ehler-Danlos syndrome

Non-Syndromic Familial TBAD

- Family history of aortic/arterial aneurysm/dissection, or
- sudden death in 1st or 2nd degree relative
- absence of known syndrome

RESULTS

28%

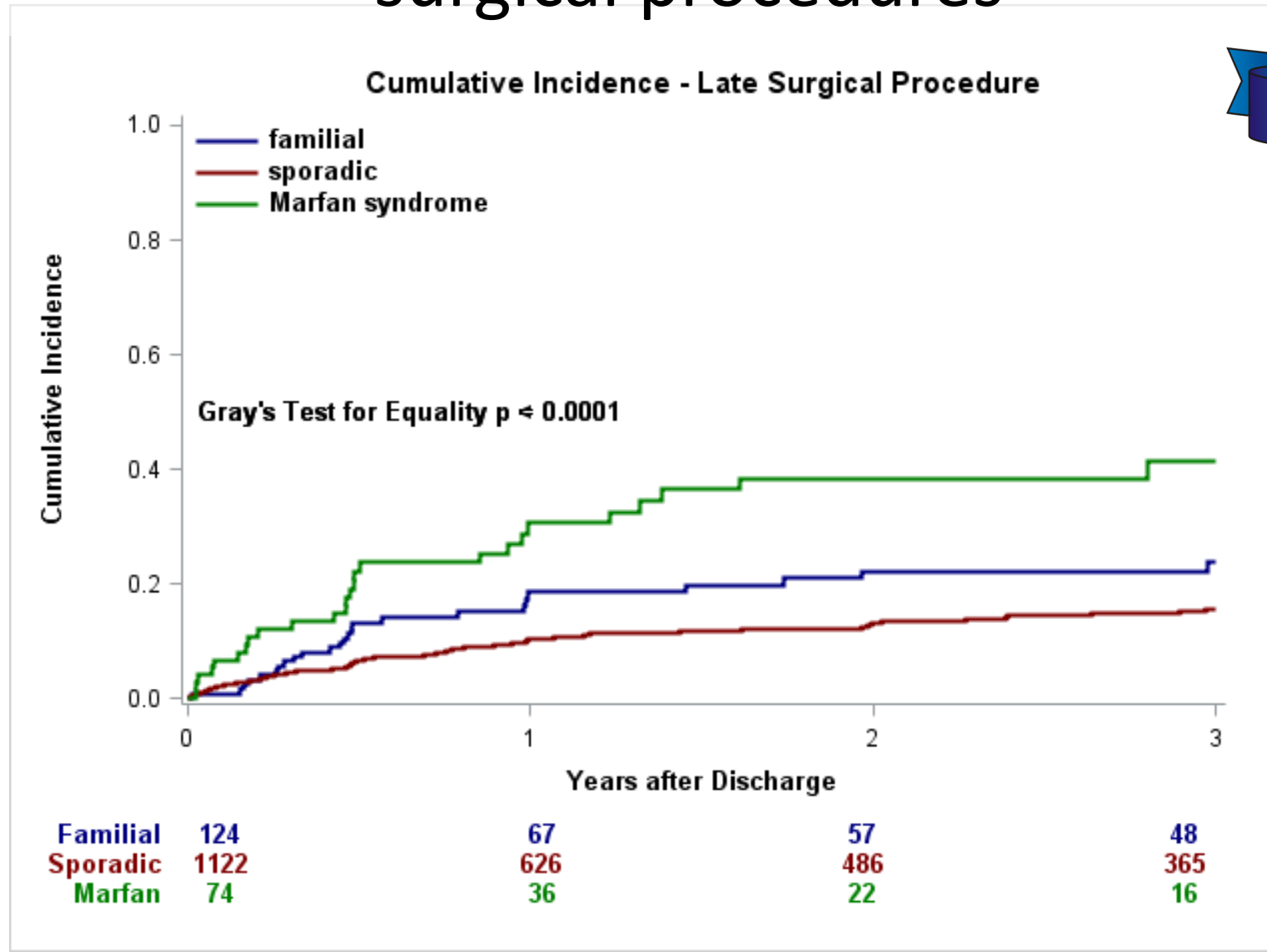
Heritable etiology of TBAD*

9.6% Syndromic
18.3% Non-syndromic familial

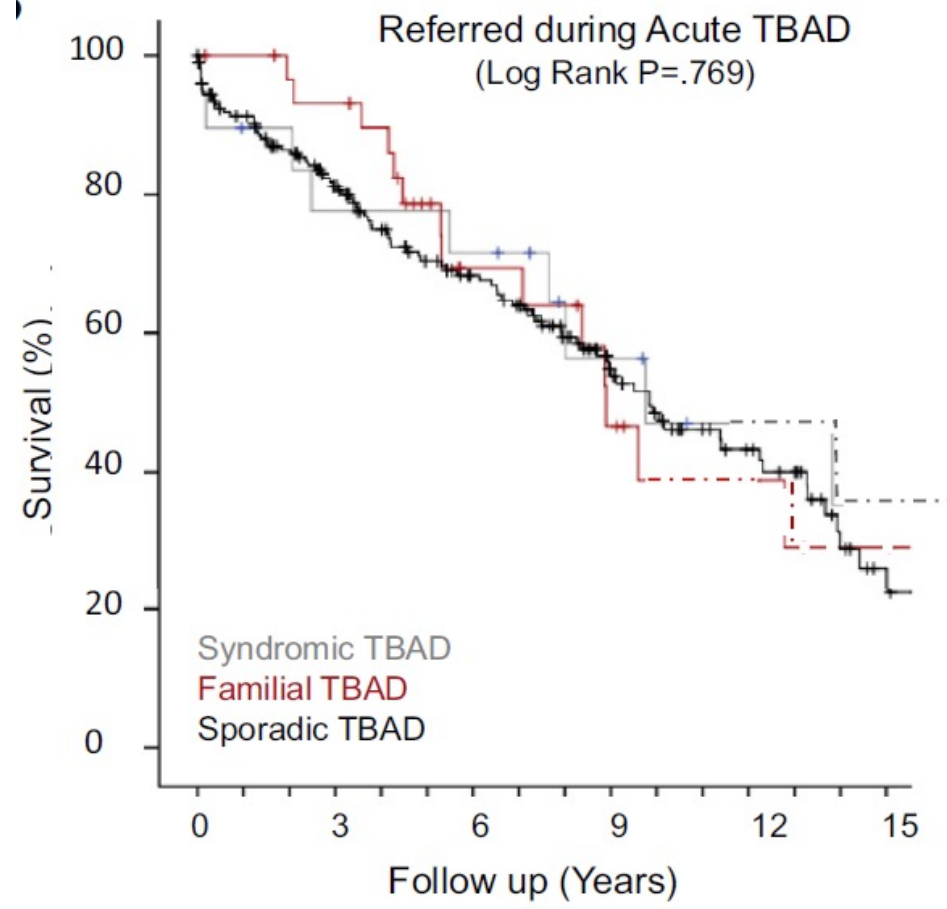
*Many shared clinical features:

- Presentation at younger ages
- Dissection with lower blood pressures
- More retrograde aortic dissections post TEVAR
- Death at younger ages vs sporadic TBAD

Non-syndromic familial TBAAD patients require more late surgical procedures

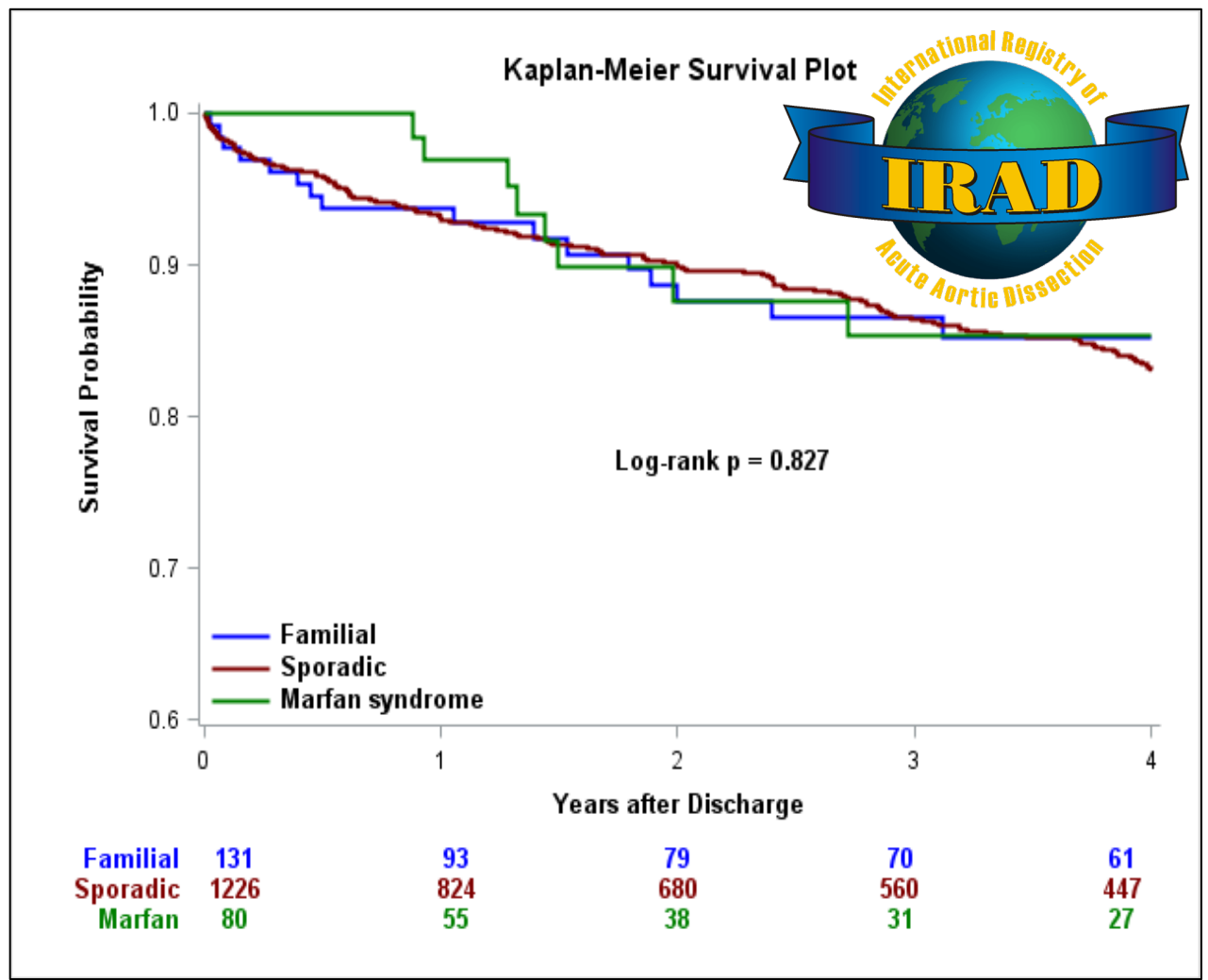


Premature aging of the aorta



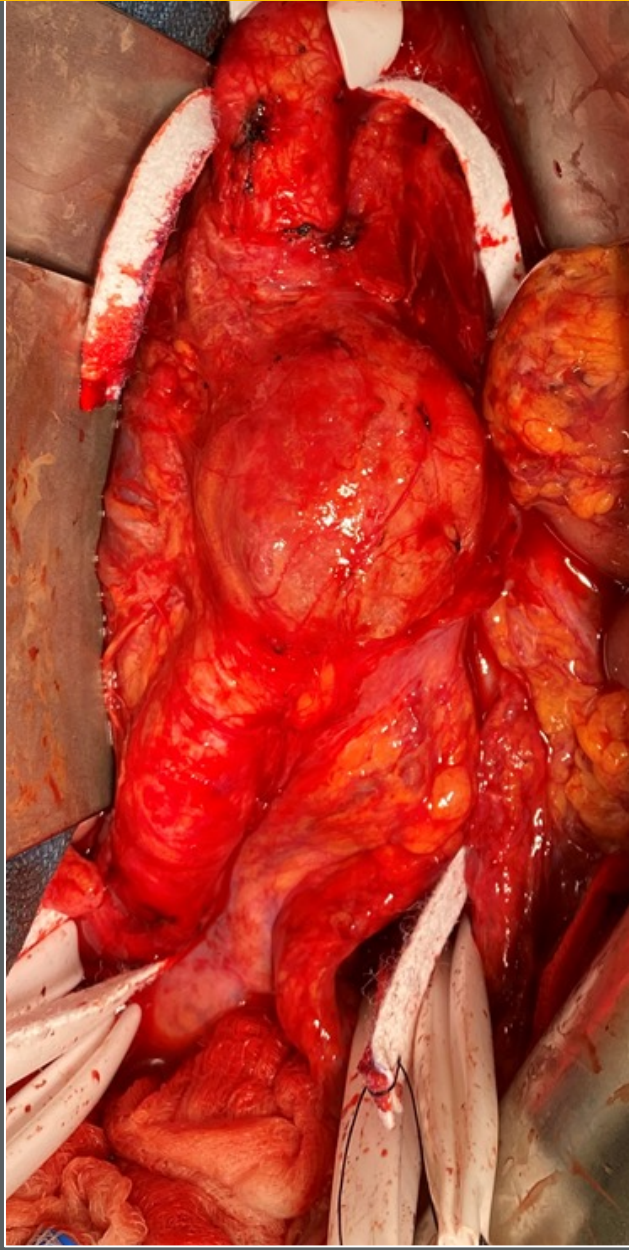
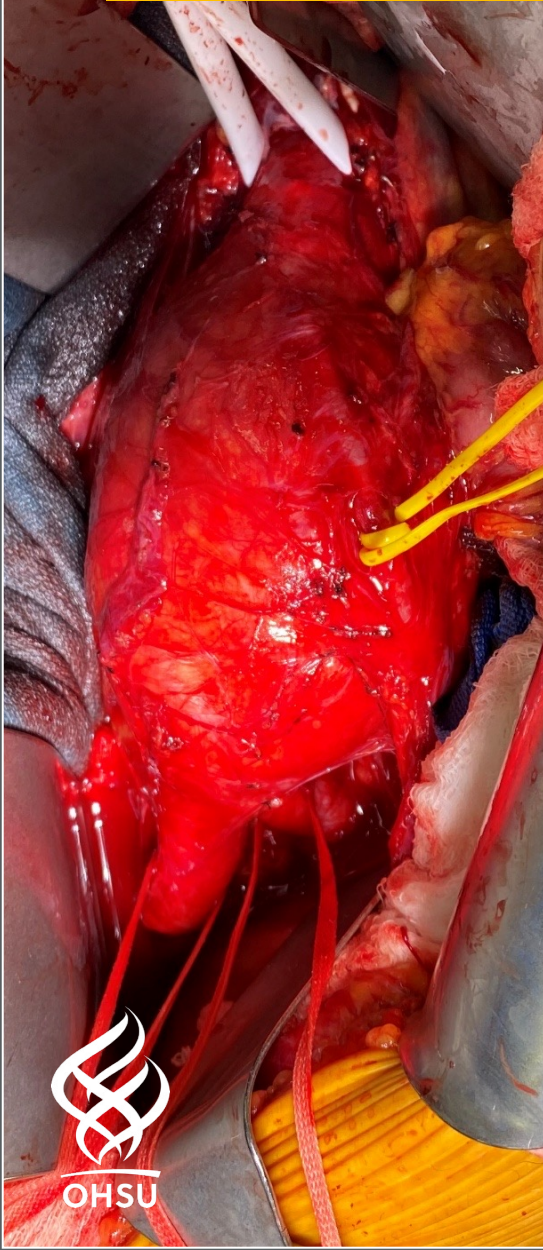
Number at Risk	19	13	12	7	4	3
	31	27	13	8	5	2
	202	136	96	56	28	7

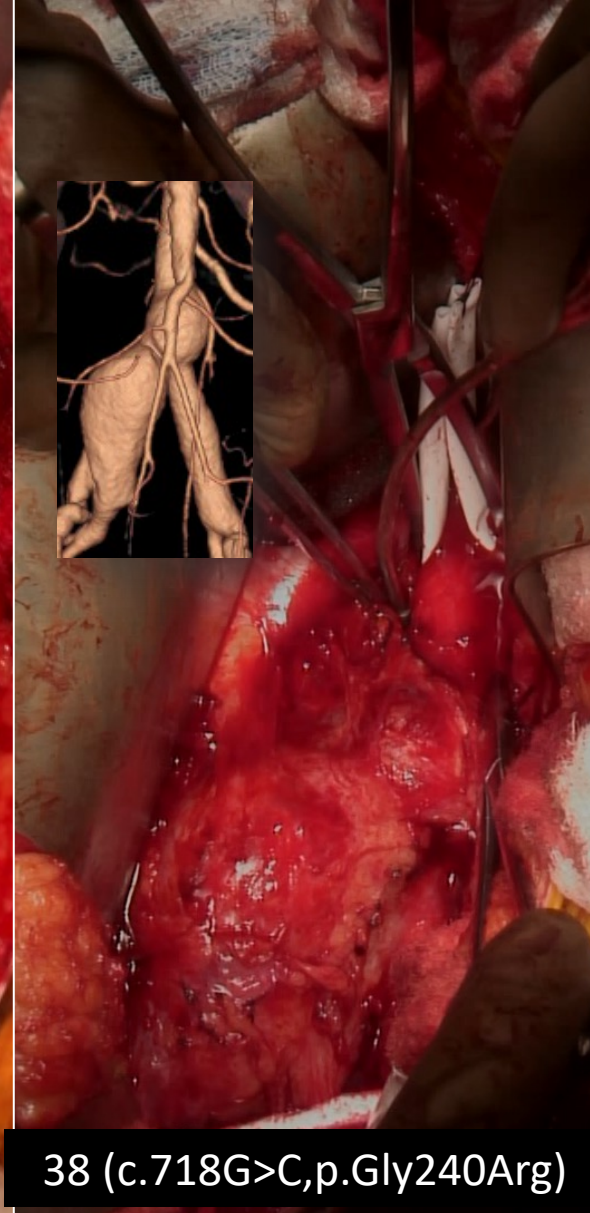
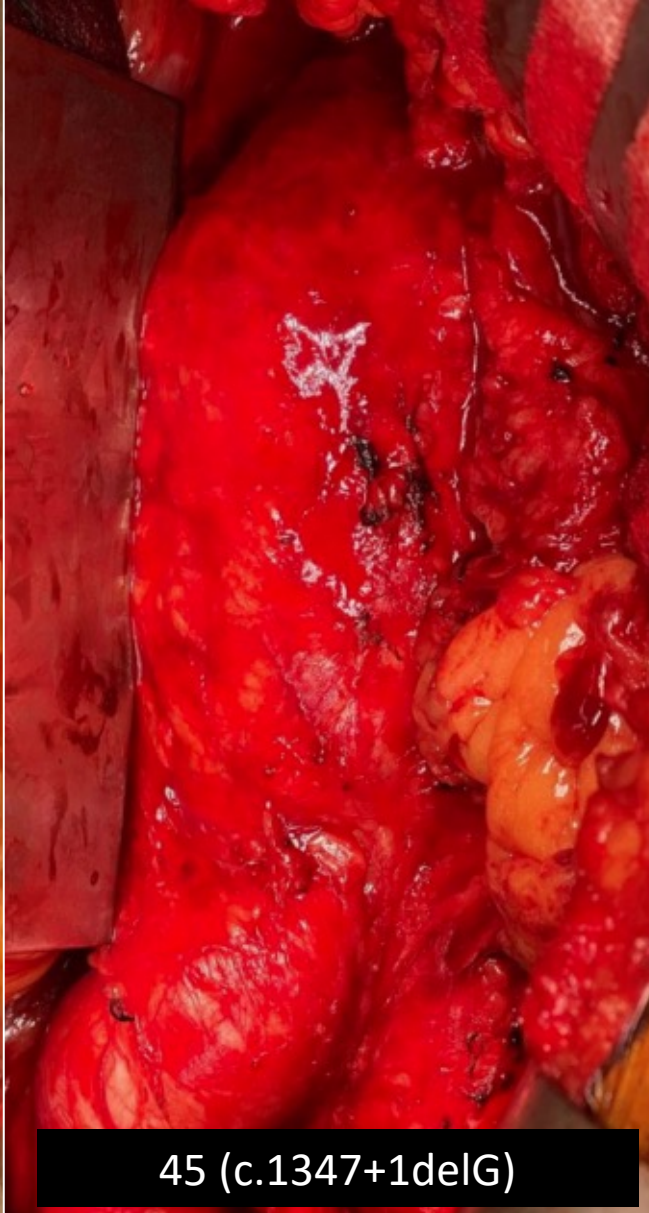
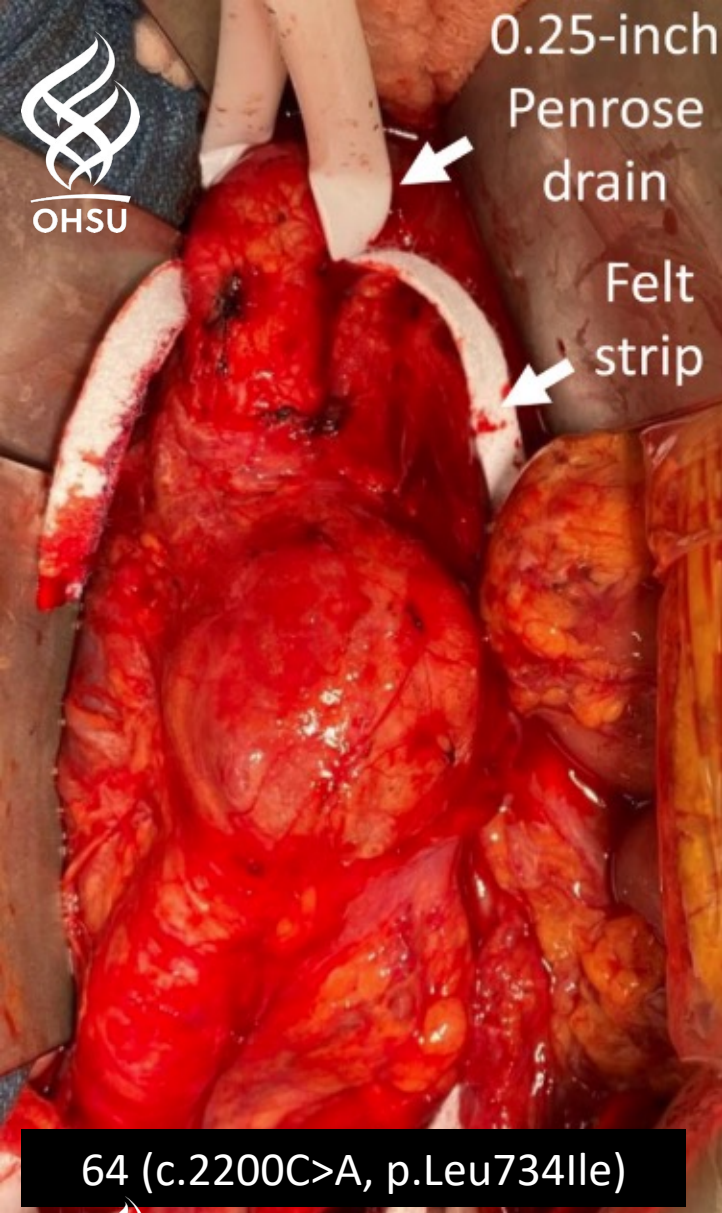
Similar survival outcomes at 4 years between groups



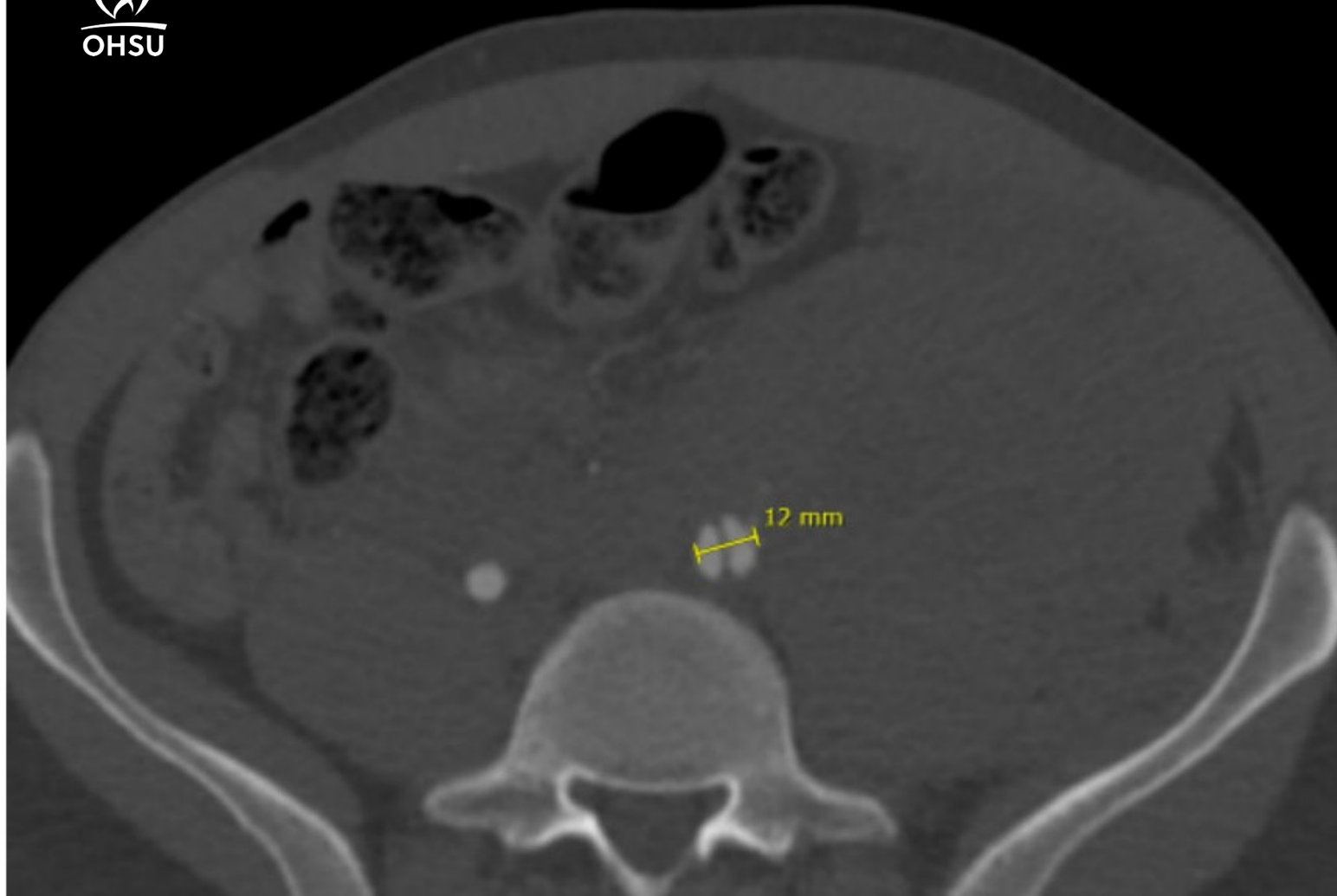
Familial	131	93	79	70	61
Sporadic	1226	824	680	560	447
Marfan	80	55	38	31	27

Not All Aortas Are Created Equal





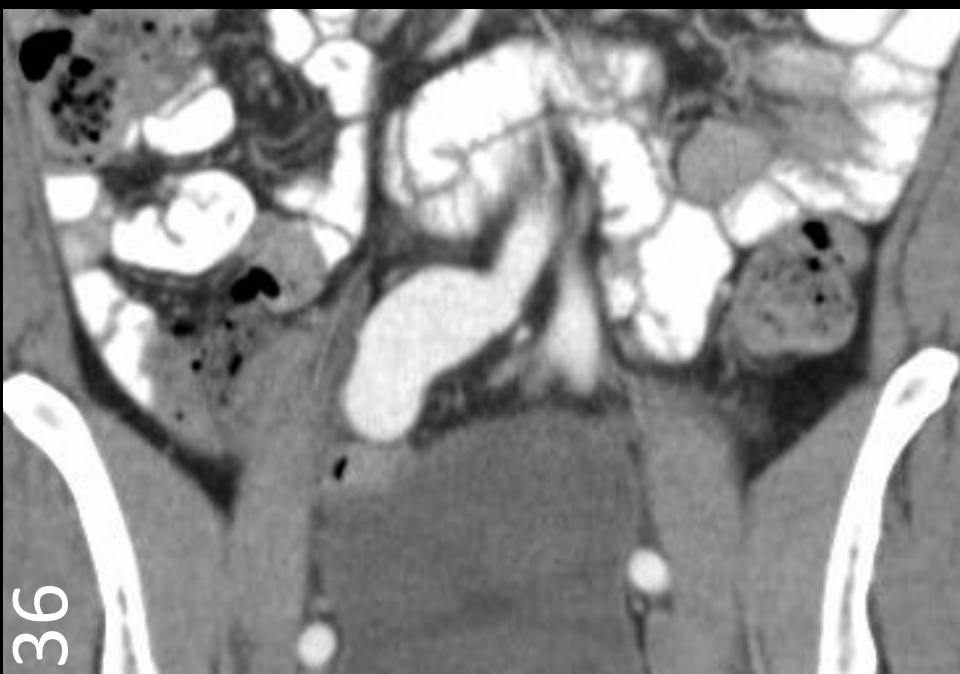
There is variability in tissue quality Genotype-Surgical Phenotype Correlation



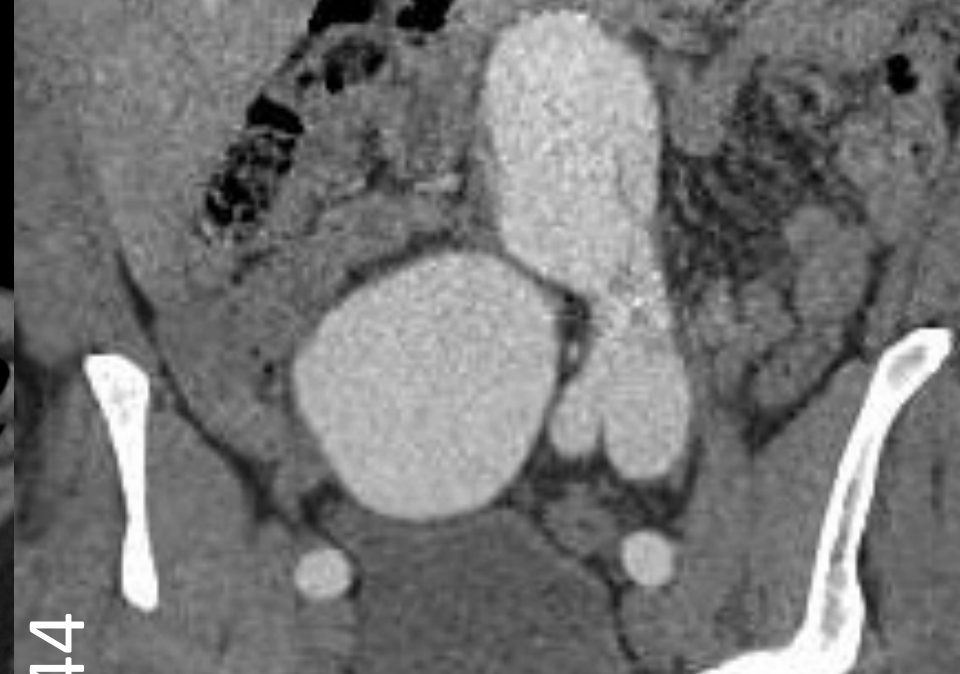
COL3A1 (c.1347+1G>A)



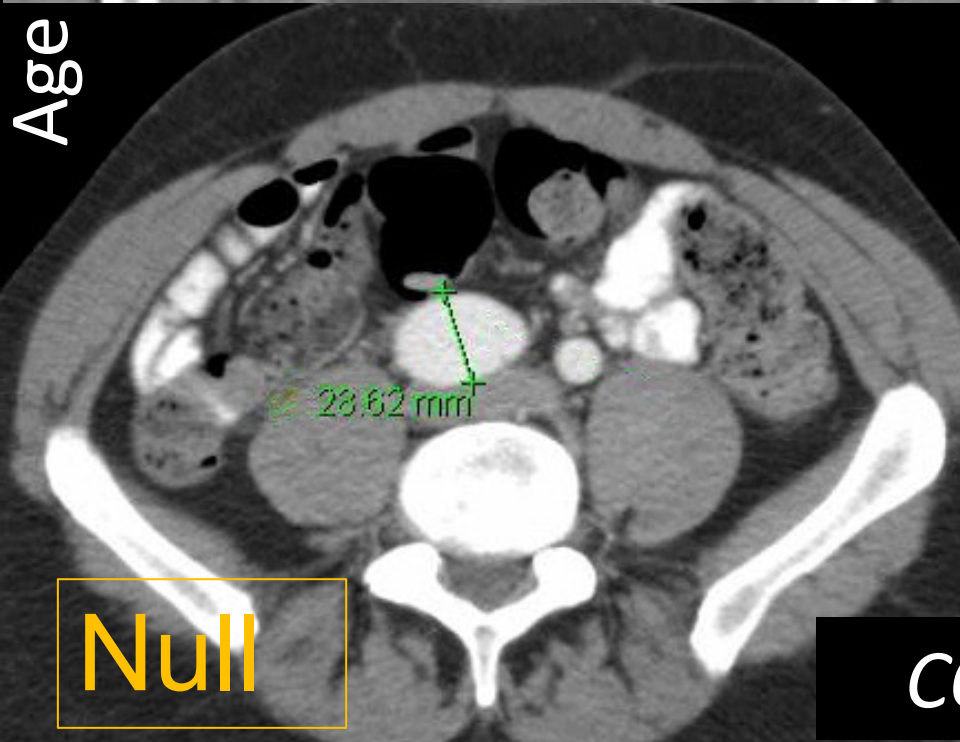
COL3A1 c.2735G>A, p.Gly0912Asp



Age 36

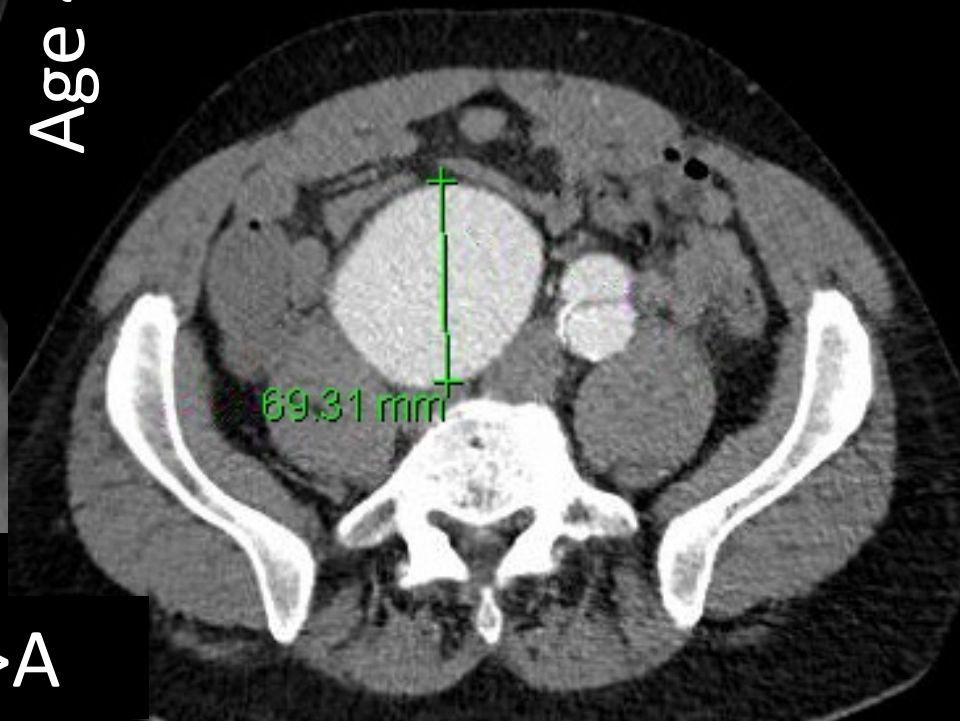


Age 44



Null

COL3A1 c.852+1 G>A





OHSU

TEVAR in fragile tissues

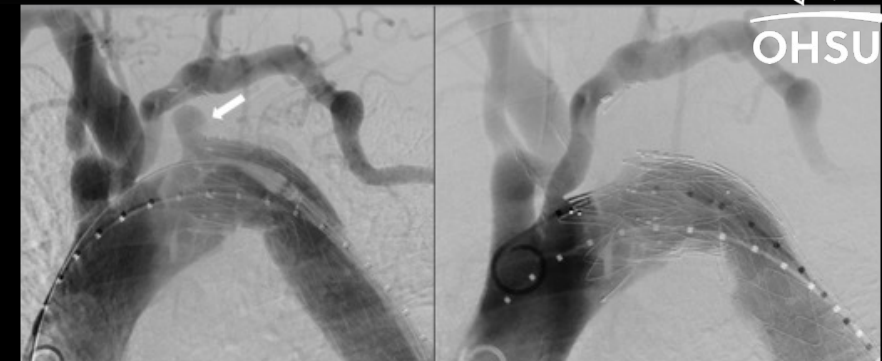
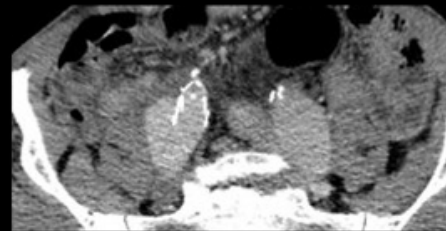
Device fixation failure in the diseased aorta

- Degeneration of the native aorta at the landing zone (device radial force)
- Device migration/erosion
- New dissections
 - Retrograde aortic dissection (RTAD)
 - Stent graft–induced new entry tears



49-year-old male with LDS type type III (*SMAD3*, c.1009+2T>A IVS7+2T>A)

TEVAR (Cook TX2)
Medtronic Navion (type 1a endoleak)
Abd debranching, EVAR
L IBE branched iliac graft (type 1b)



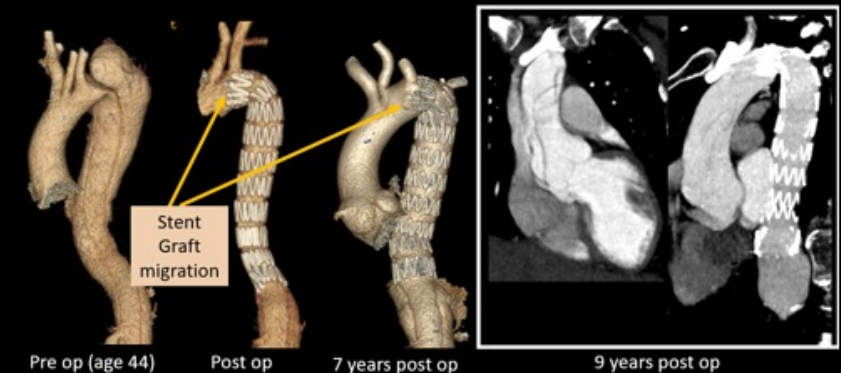
49 yo male *SMAD3*, c.1009+2T>A IVS7+2T>A)

TEVAR (Cook TX2) Medtronic Navion (type 1a endoleak)

Stent graft–induced new distal entry tears (SINE)



Delayed retrograde aortic dissection in 53F with MFS (clinical diagnosis)



***FBN1* & *TGFβ* pathway: aortic arch is an unstable landing zone for current TEVAR technology**



genTAC

Endovascular thoracic aortic repair in confirmed or suspected genetically triggered thoracic aortic dissection

Sherene Shalhub, MD, MPH,^a Kim A. Eagle, MD,^b Federico M. Asch, MD,^c Scott A. LeMaire, MD,^{d,e} and Dianna M. Milewicz, MD, PhD,^f on behalf of the GenTAC Investigators for the Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC) Consortium, *Seattle, Wash; Ann Arbor, Mich; Washington, D.C.; and Houston, Tex*

August 2018

REVIEW ARTICLE

Braz J Cardiovasc Surg 2020 -

The Role of Thoracic Endovascular Aortic Repair (TEVAR) of Thoracic Aortic Diseases in Patients with Connective Tissue Disorders – A Literature Review

Amer Harky¹, MBChB, MSc, MRCS; Syed Mohammad Asim Hussain¹, MBChB, MSc, MRCS; Beverly MacCarthy-Ofosu¹, MBChB, BSc; Mohammad Usman Ahmad³, MBChB

JAMA Surgery | Original Investigation

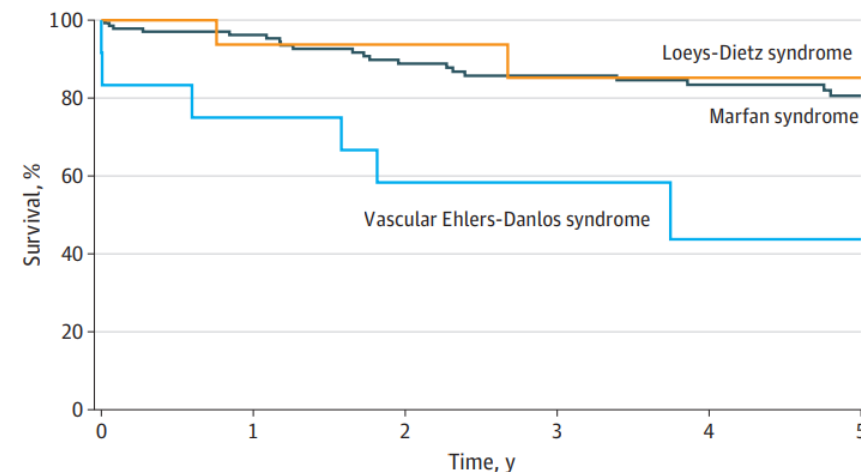
Outcomes After Endovascular Aortic Intervention in Patients With Connective Tissue Disease

Karl Wilhelm Olsson, MD, PhD; Kevin Mani, MD, PhD; Anne Burdess, MD, PhD; Suzannah Patterson, BS; Salvatore T. Scali, MD; Tilo Kölbel, MD, PhD; Giuseppe Panuccio, MD, PhD; Ahmed Eleshra, MD; Luca Bertoglio, MD; Vincenzo Ardita, MD, PhD; Germano Melissano, MD; Amish Acharya, MD; Colin Bicknell, MD;

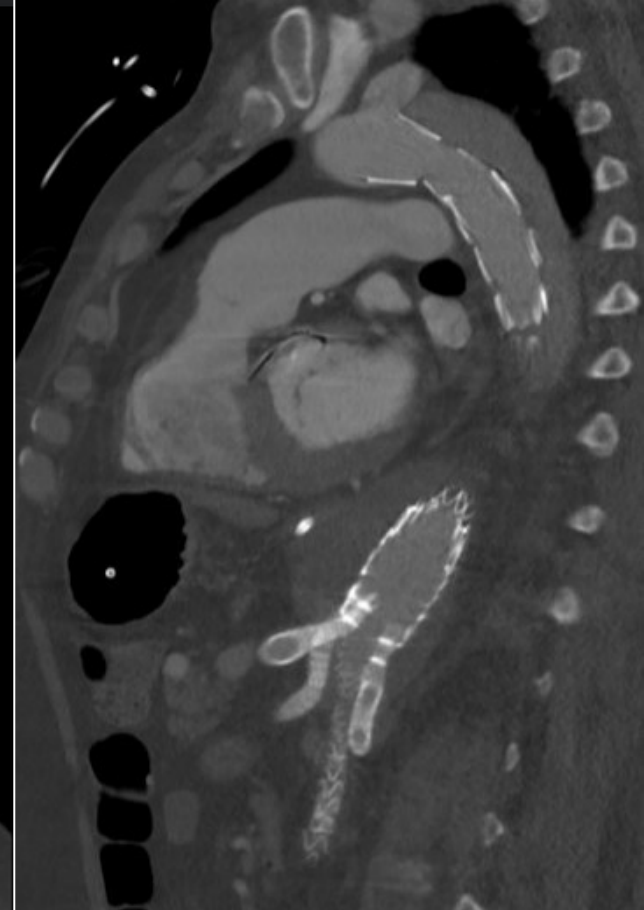
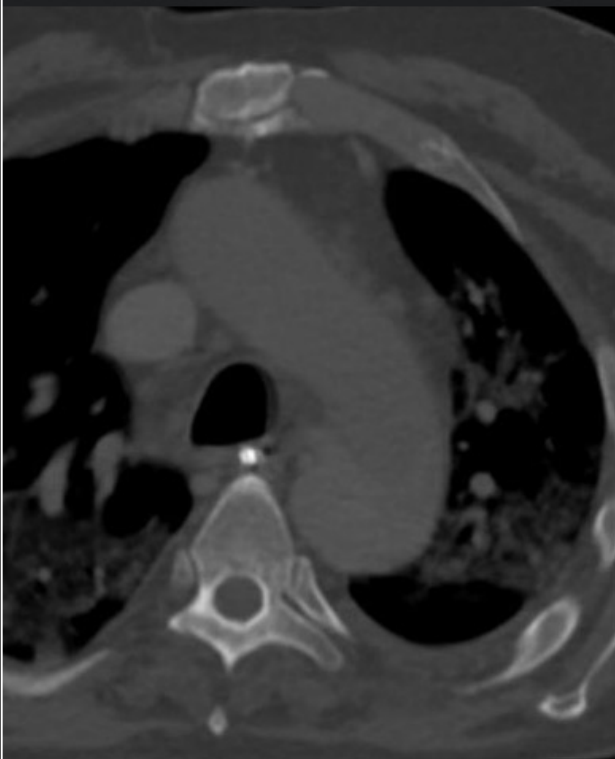
Endovascular Aortic Intervention in Patients With Connective Tissue Disease (EVICTUS)

- N=171 (2005-2020)
- 18 aortic centers in Europe, Asia, North America, & New Zealand.
- Marfan syndrome: Clinical diagnosis
- Loeys-Dietz syndrome: genetic testing
- VEDS: Clinical diagnosis
- Median follow-up: 4.7 years (1.9-9.2)

Figure. Kaplan-Meier Estimate of Survival for Patients With Connective Tissue Disease After Endovascular Treatment of Aortic Pathology



No. at risk	142	110	92	81	69	57
Marfan syndrome	17	15	12	11	7	4
Loeys-Dietz syndrome	12	10	8	7	4	3
Vascular Ehlers-Danlos syndrome						



55-year-old man
with MFS (*FBN1*
c.6963delG,
Phe2322Leufs*76
, null variant)



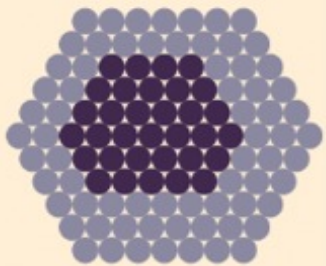
Characterization of syndromic, nonsyndromic familial, and sporadic type B aortic dissection

Sherene Shalhoub, MD, MPH, Jasmine Y. Rah, BA, Rebecca Campbell, BS, Matthew P. Sweet, MD, MS, Elina Quiroga, MD, and Benjamin W. Starnes, MD, FACS, Seattle, Wash



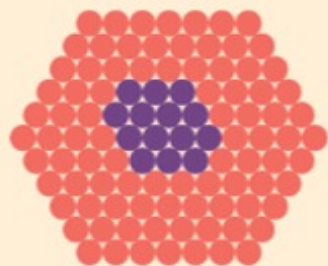
MORE Retrograde Aortic Dissections post TEVAR 115 TEVARs

SynTBAD



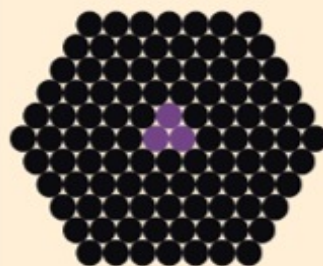
33%

FTBAD



15%

SpTBAD



3%



P= .006

Mean follow up 7.1 ± 5.4 years

J Vasc Surg. 2021 Jun;73(6):1906-1914

2022 ACC/AHA Guideline for the Diagnosis & Management of Aortic Disease: **Gene-Specific Approach**

Marfan Syndrome

2a	C-LD	4. In patients with Marfan syndrome who have undergone aortic root replacement, surveillance imaging every 3 to 5 years for potential AAA is reasonable. ^{2,29}
2a	C-EO	1. In patients with Marfan syndrome and a nondissected aneurysm of the aortic arch, descending thoracic aorta , or abdominal aorta of ≥ 5.0 cm , surgical intervention to replace the aneurysmal segment is reasonable.

Loeys Dietz Syndrome

1	C-LD	3. In patients with Loeys-Dietz syndrome, a baseline MRI or CT from head to pelvis is recommended to evaluate the entire aorta and its branches for aneurysm, dissection, and tortuosity. ¹⁻⁴
2a	C-EO	4. In patients with Loeys-Dietz syndrome without dilation of the aorta distal to the aortic root or ascending aorta and without dilated or dissected arterial branches, surveillance imaging from chest to pelvis with MRI (or CT every 2 years) is reasonable, but imaging may be more frequent depending on family history.
2b	C-EO	2. In patients with Loeys-Dietz syndrome attributable to a pathogenic variant in <i>TGFBR1</i> , <i>TGFBR2</i> , or <i>SMAD3</i> , surgery to replace the intact aortic arch, descending aorta, or abdominal aorta at a diameter of ≥ 4.5 cm may be considered, with the specific genetic variant, patient age, aortic growth rate, family history, presence of high-risk features (Table 11), and surgical risk informing the decision.

- Risk factor modification: smoking cessation, HTN therapy, avoid fluoroquinolones
- Surveillance
- Operative planning/techniques



Biologically Informed Surgical Decision-Making

- Age
- Prior operations
- Cardiac function
- Frailty / other comorbid conditions
- Genotype-surgical phenotype
- Biological twinning

Genotype-surgical phenotype
and how this impacts surgical decision making



When does the benefit of open repair outweigh the risk of long-term endovascular secondary interventions & failure?



OHSU NW GAAP Northwest Genetic Aortopathy & Arteriopathy Program



Multidisciplinary approach to precision surgery

- MFS/ LDS / VEDS / VEDS like conditions
- Smooth muscle cell aortopathies
- Turner syndrome
- Middle aortic syndrome
- Heritable aortopathy
- FMD/SAM

Comprehensive Care Plan



DIAGNOSIS



MEDICAL MANAGEMENT



SURVEILLANCE



REPAIR THRESHOLD



OPTIMAL REPAIR METHODOLOGY

NW GAAP SYMPOSIUM: Living Better with Marfan, Loeys-Dietz, & VEDS

Saturday, May 11, 2024
Portland, Oregon

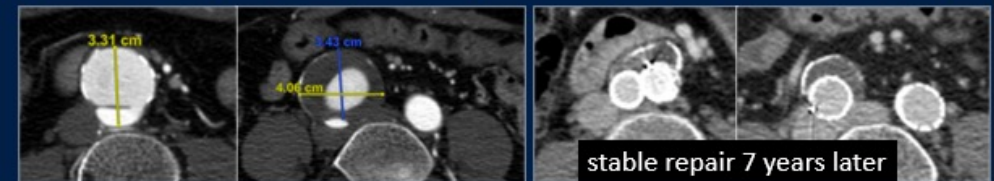
THE MARFAN FOUNDATION



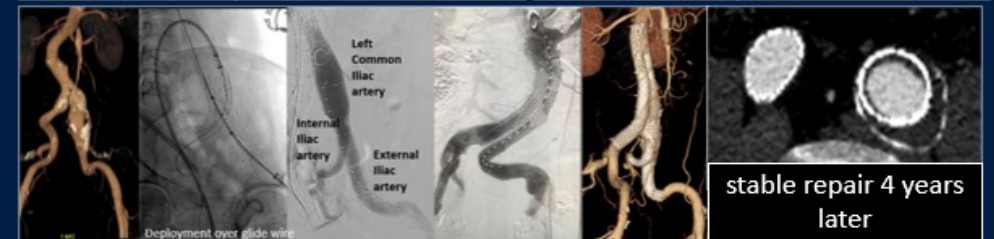
Biological twinning & Shared Decision Making

Using pre-existing data from family members (or similar variants)

60-year-old female



65-year-old male



VEDS COL3A1 c.555delT p.Gly186Valfs*36, Null variant

Shalhoub & Byers. J Vasc Surg Cases Innov Tech. 2023 Apr 20;9(2):101192

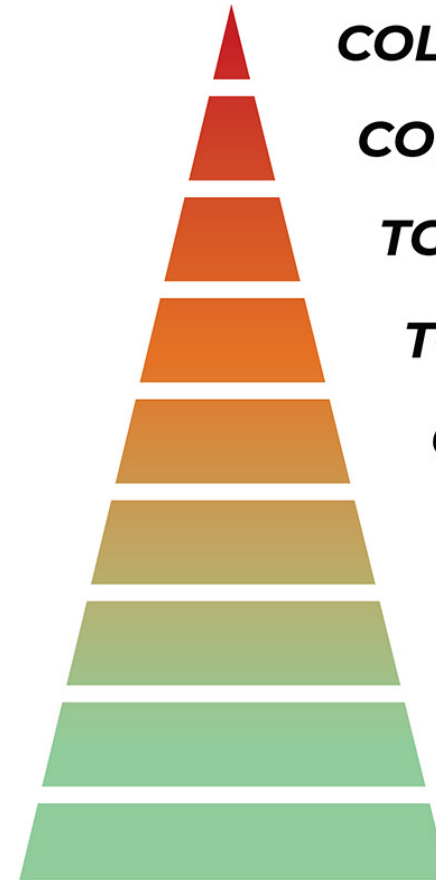
Genotype-Surgical Phenotype Correlation:

Genetic Variant and Type of Variant is Associated with
Tissue Integrity = Precision Vascular Surgery

CONCEPTUAL MODEL

Aortic disease
exists on a
spectrum of
vulnerability

TISSUE INTEGRITY



COL3A1 large amino acid substitution

COL3A1 small amino acid substitution

TGFBR2

TGFBR1

COL3A1 null

SMAD3

TGFb2 / TGFb3

FBN1 null

FBN1

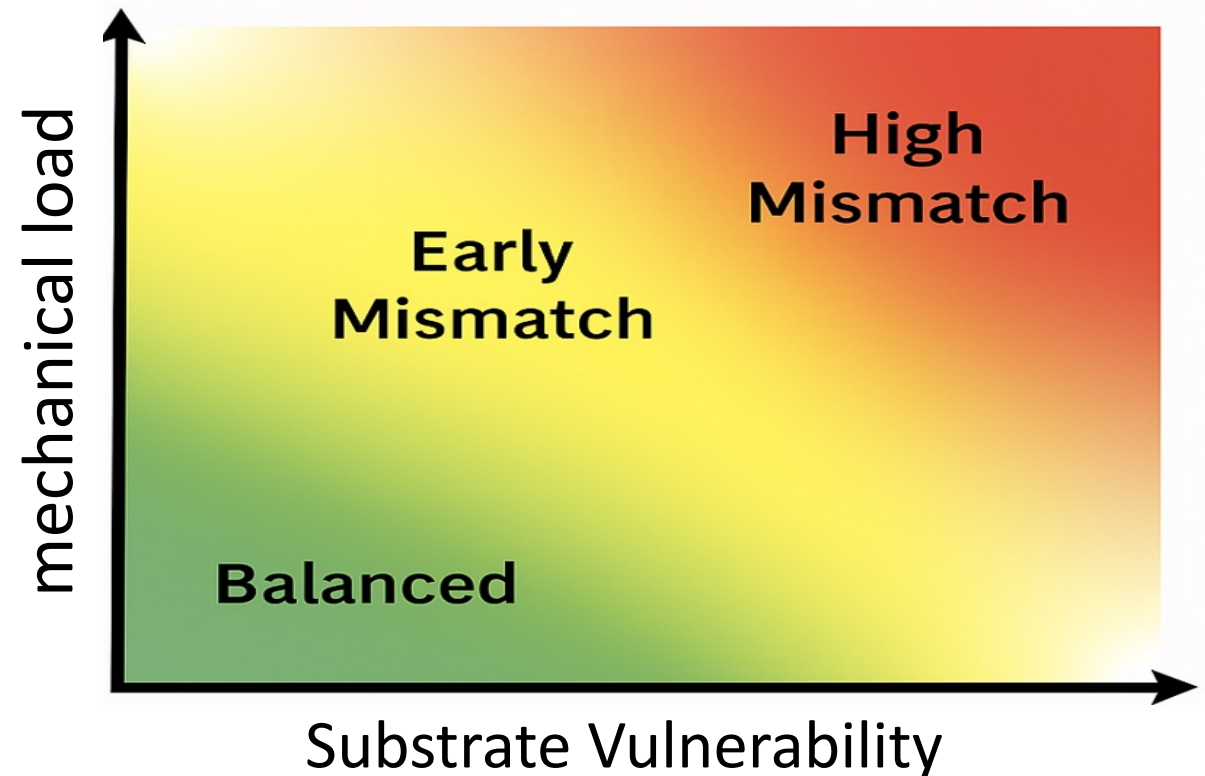
Endovascular repair relies on exclusion and aortic remodeling (which is variable)

Degeneration of the native aorta at the landing zone (device radial force)

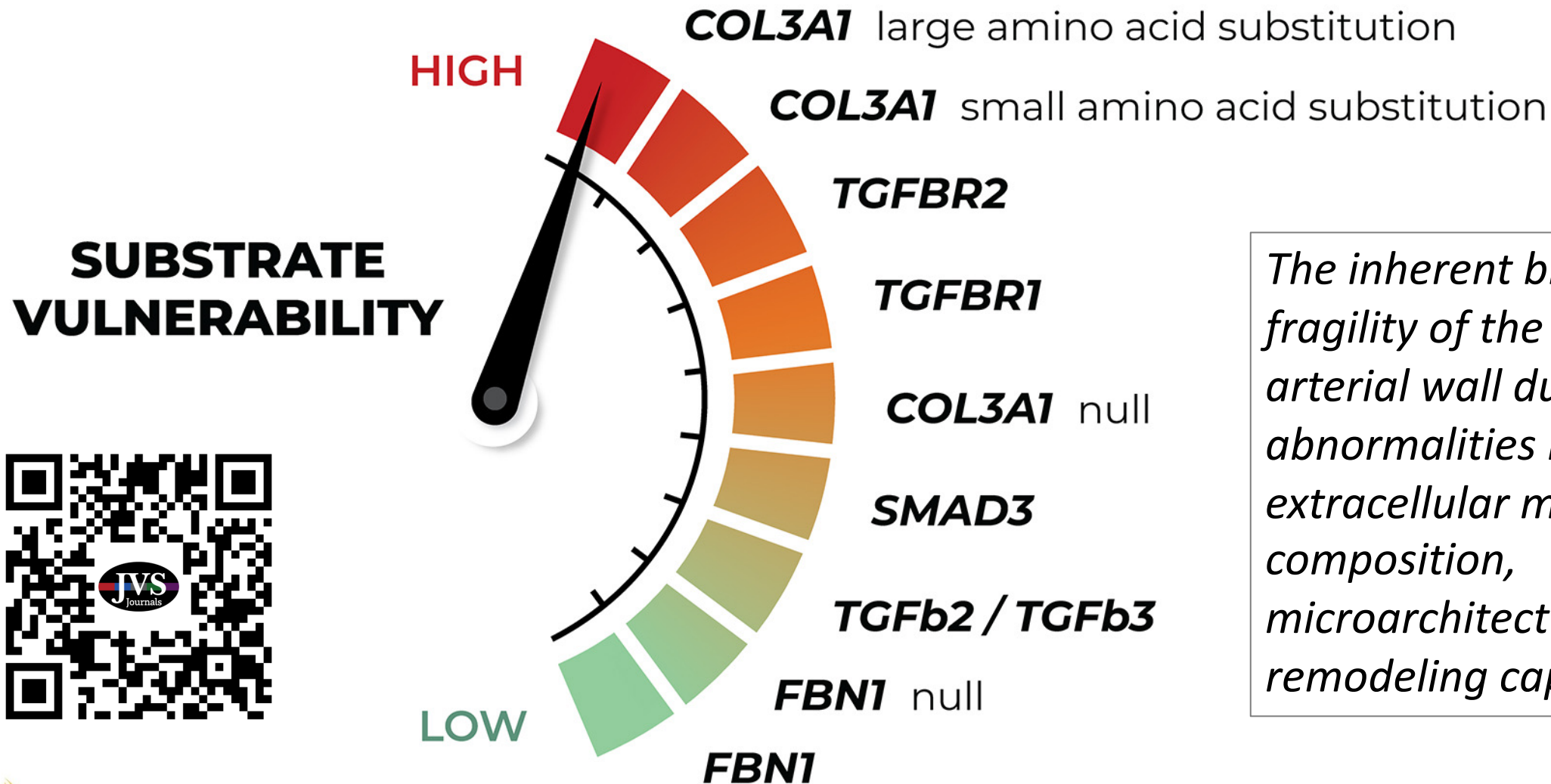
Device migration/erosion

New dissections, e.g., RTAD

Device-Substrate-Mismatch



Aortic disease exists on a spectrum of vulnerability



The inherent biologic fragility of the aortic or arterial wall due to abnormalities in extracellular matrix composition, microarchitecture, or remodeling capacity.



Mutations in the COL3A1 gene result in the Ehlers-Danlos syndrome type IV and alterations in the size and distribution of the major collagen fibrils of the dermis

L T Smith¹, U Schwarze, J Goldstein, P H Byers

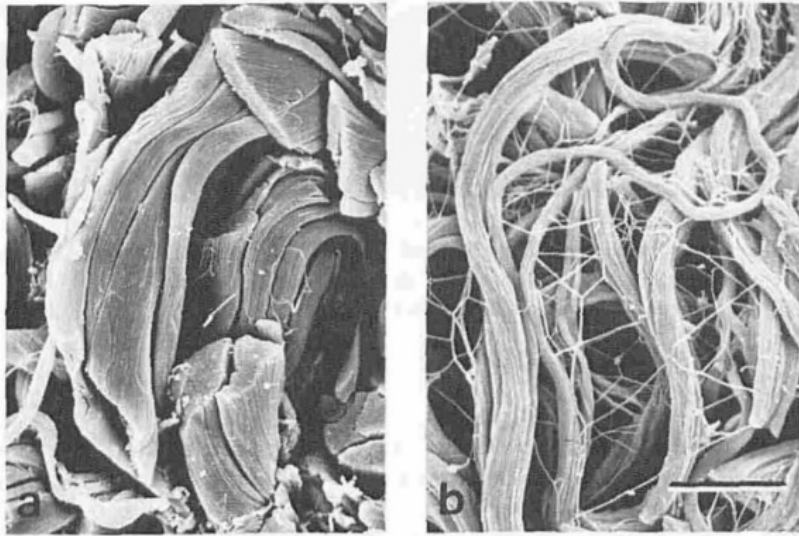
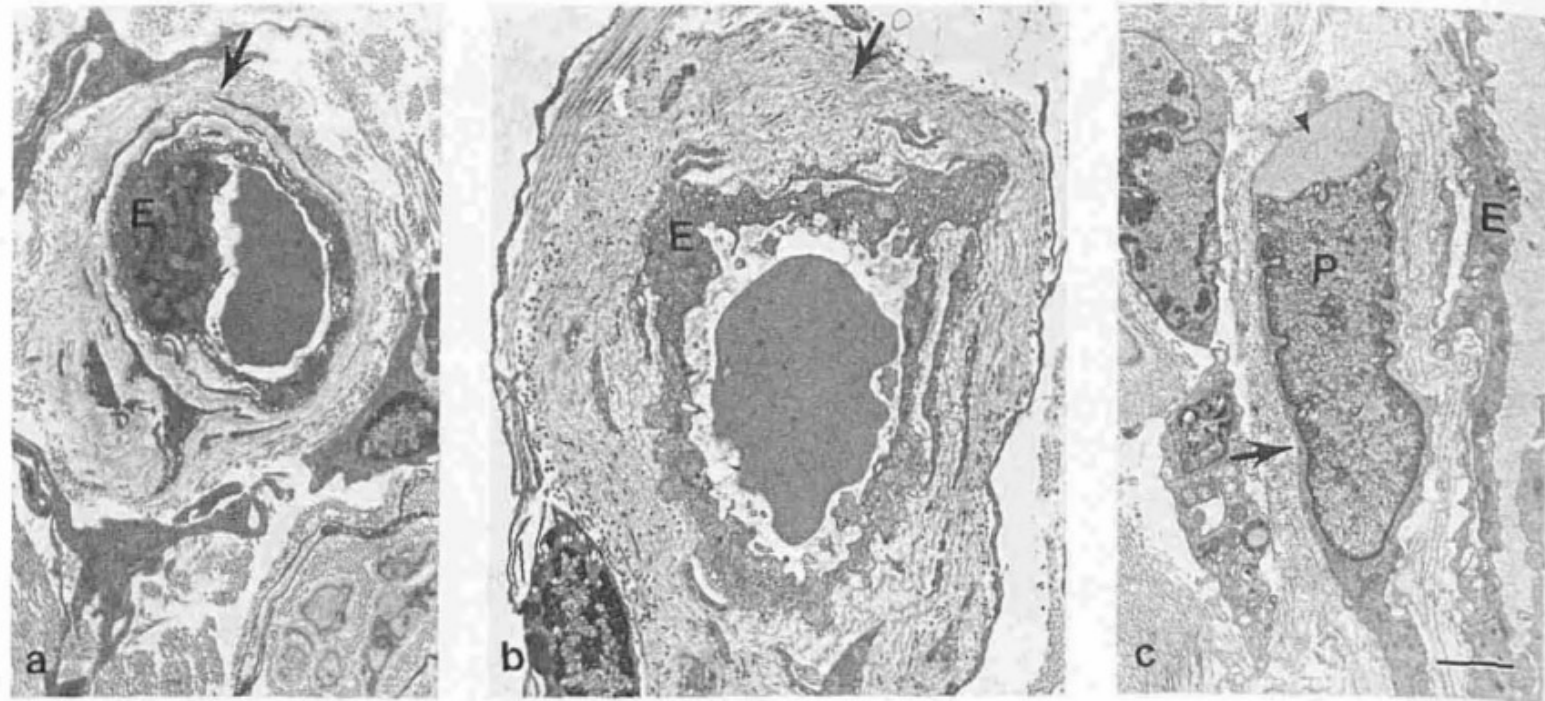


Figure 3. Dermal collagen fibers are more loosely organized in EDS type IV. Scanning electron micrographs of collagen in the reticular dermis of a control (a) and EDS type IV skin with the mutation G373R (b) show densely organized matrix in the control (a) compared to the looser and less organized collagen fibers in the EDS type IV skin (b). The collagen fibers are enmeshed in a network of fine branched elastic fibers. Scale bar, 10 μ m.

Figure 2. Dermal blood vessels are altered in EDS type IV. Electron micrographs of blood vessels in control (a) and EDS type IV skin with the mutation G034R (b) and G1021E (c) show post capillary venules. In the EDS type IV skin (b), there are increased layers of perivascular matrix compared to controls (a) ($\rightarrow$). Endothelial cells (E) appear normal in all samples. A pericyte (P) has dilated RER (c) ($\blacktriangleright$) and is within the vessel connective tissue sheath basal lamina ($\rightarrow$). Scale bar, 2 μ m.



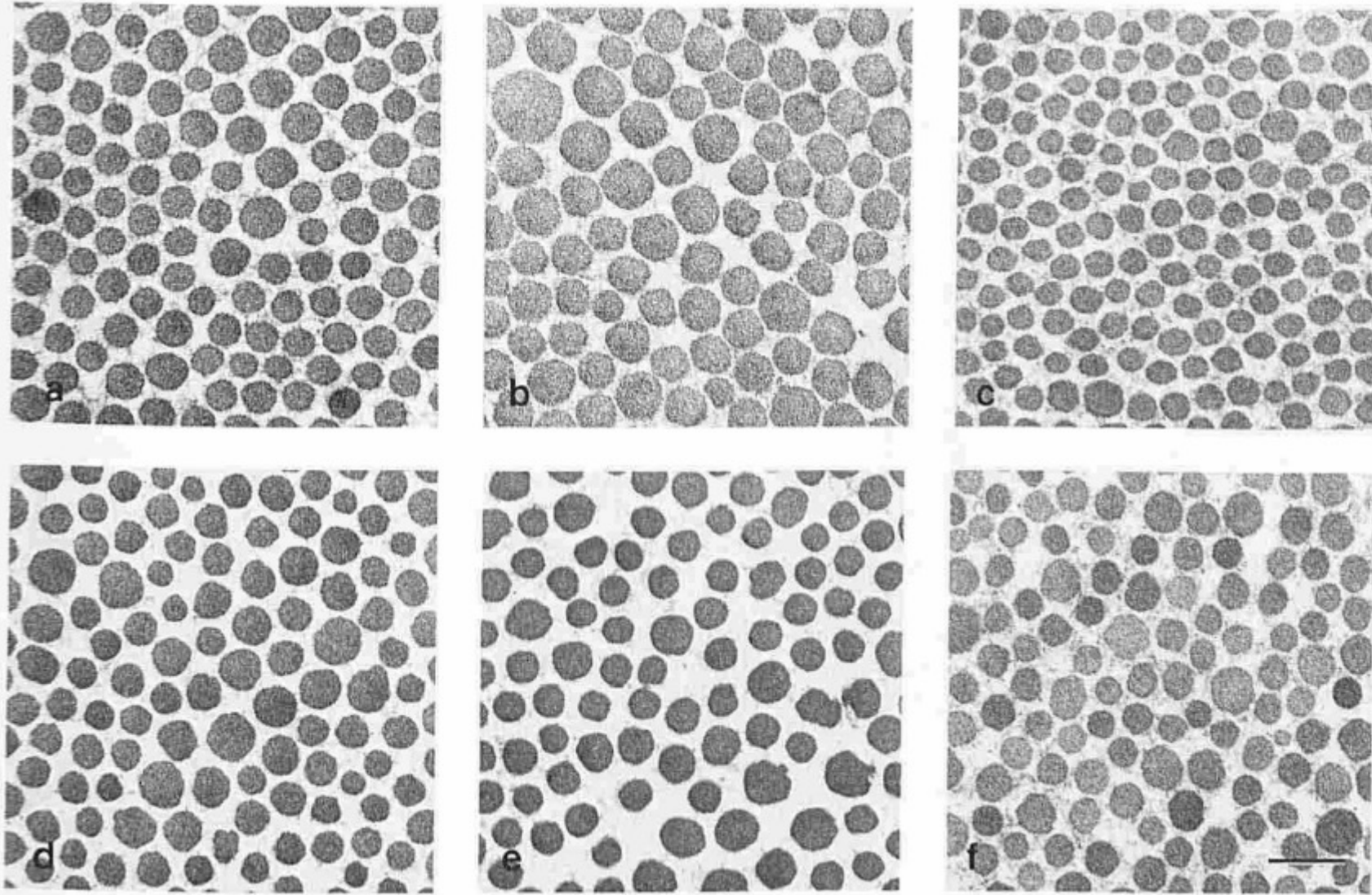
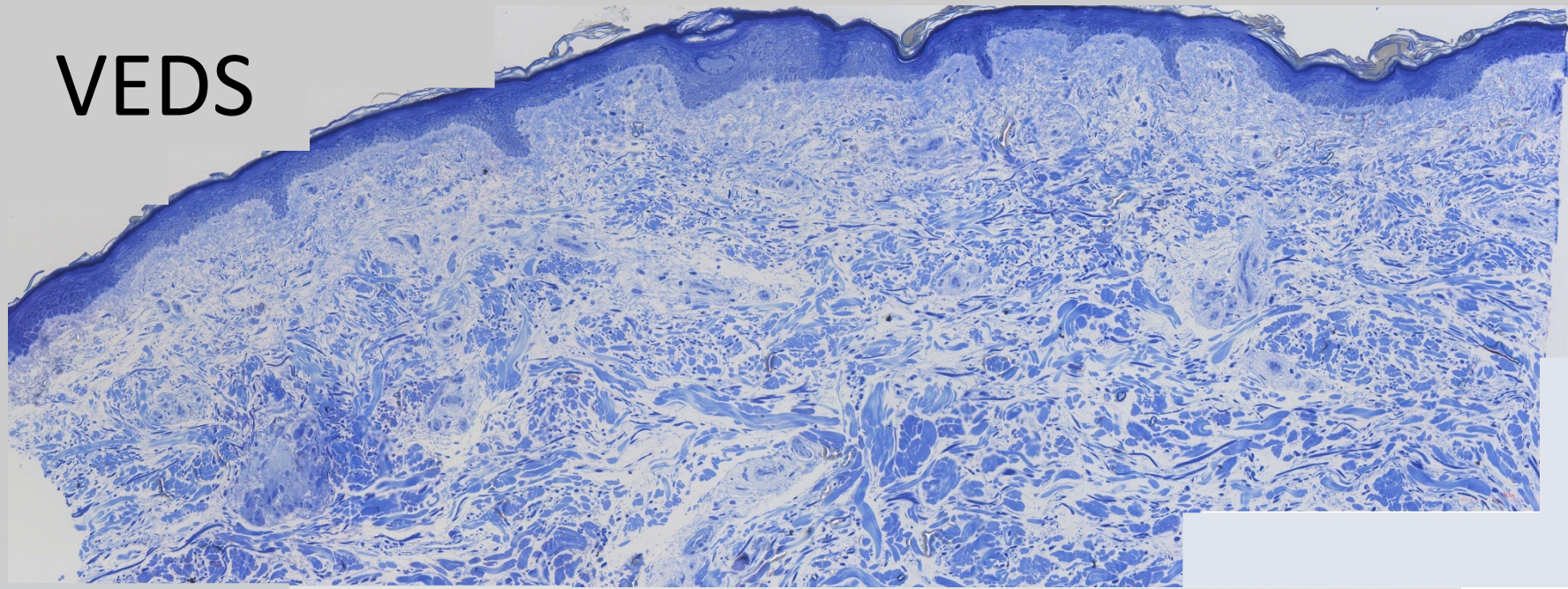


Figure 4. Collagen fibrils are variable in size and packing in EDS type IV. Transmission electron micrographs of collagen fibrils in control (a) and EDS type IV with mutations G034R (b), G1018V (c), skipping of exon 7 (d), skipping of exon 27 (e), and deletion of exons 34–48 (f) showed that control fibrils are relatively uniform in fibril diameter, shape, and packing (a). In skin from the individuals with EDS type IV, fibrils are smaller (c) or more variable in size and larger than controls (b,d–f). Distorted fibrils with noncircular cross-sections are also present in EDS type IV (d,e). Scale bar, 0.2 μm .

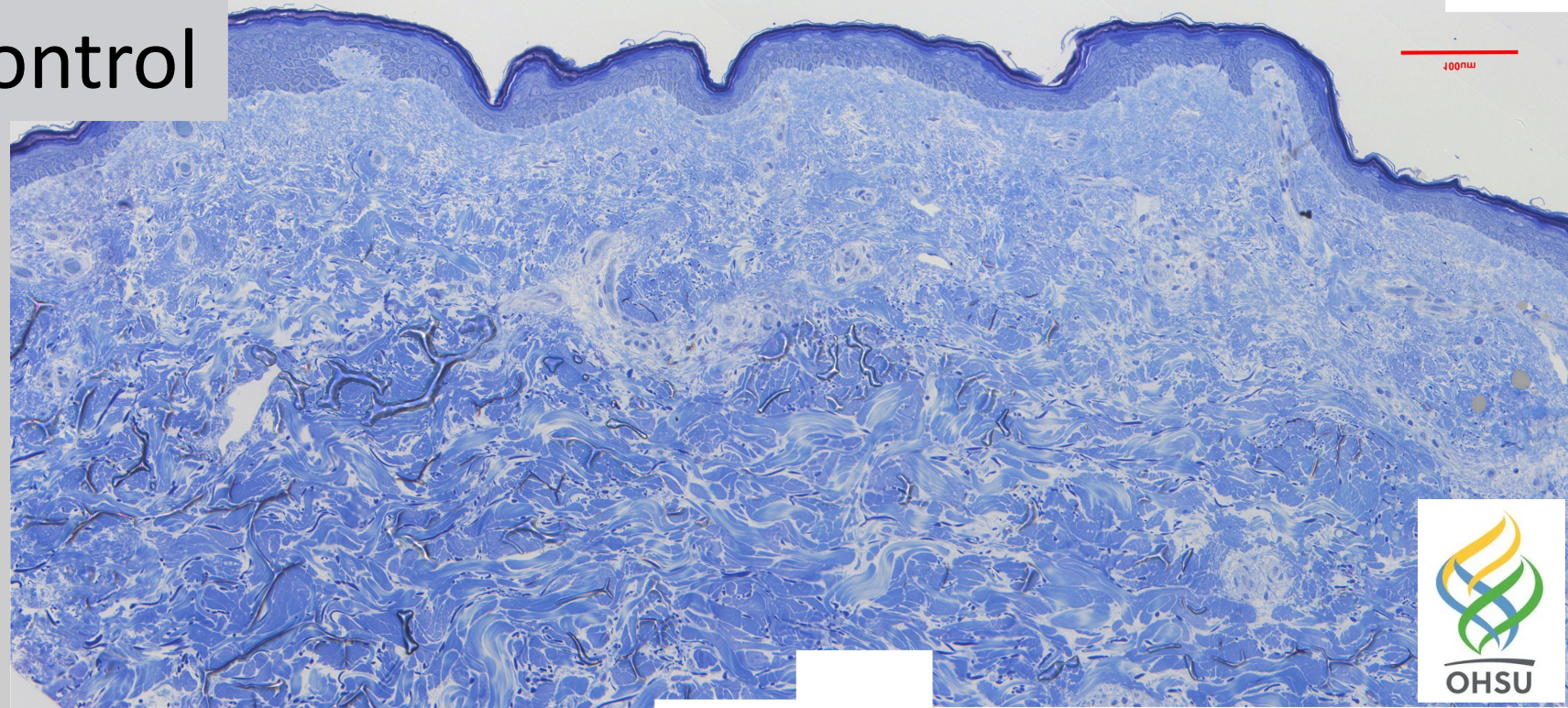
Light microscopy

- Thinner epithelium
- Broad papillary dermis
- Lack of reticular dermis large fiber bundles
- Rete ridges are deeper in the control.
- More open space throughout the dermis compared to space filling collagen fiber bundles in the control.
- Though not obvious with this staining, leucocytes are more common in the VEDS dermis than control.

VEDS



control



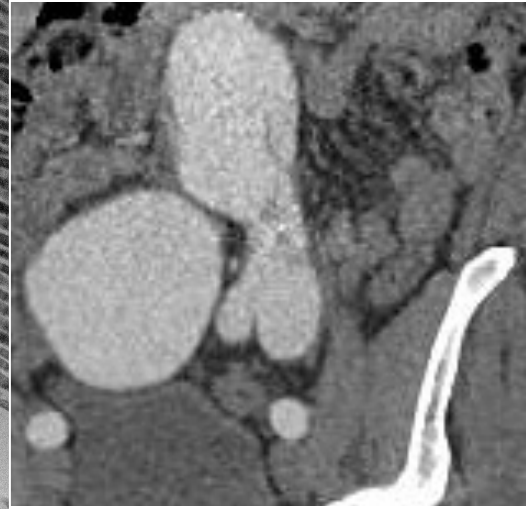
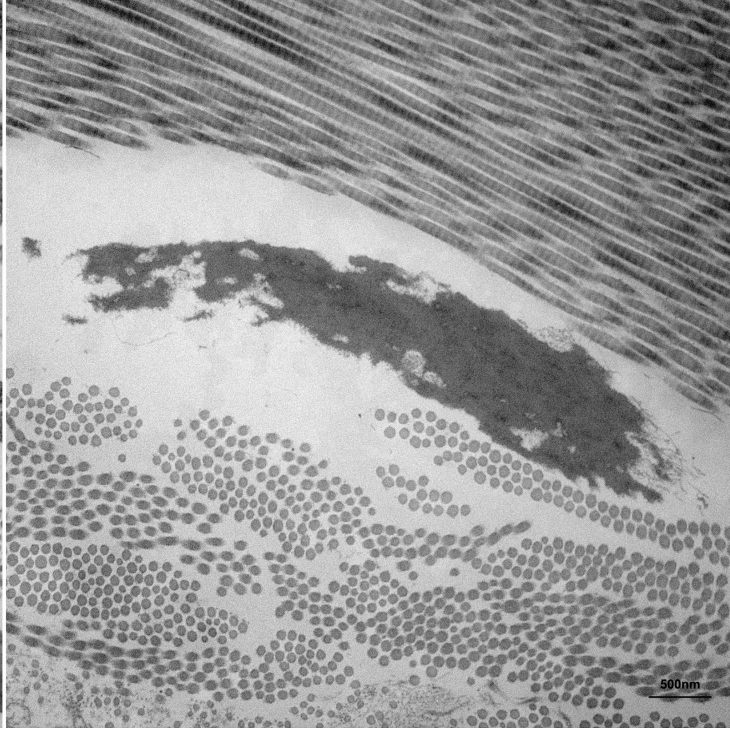
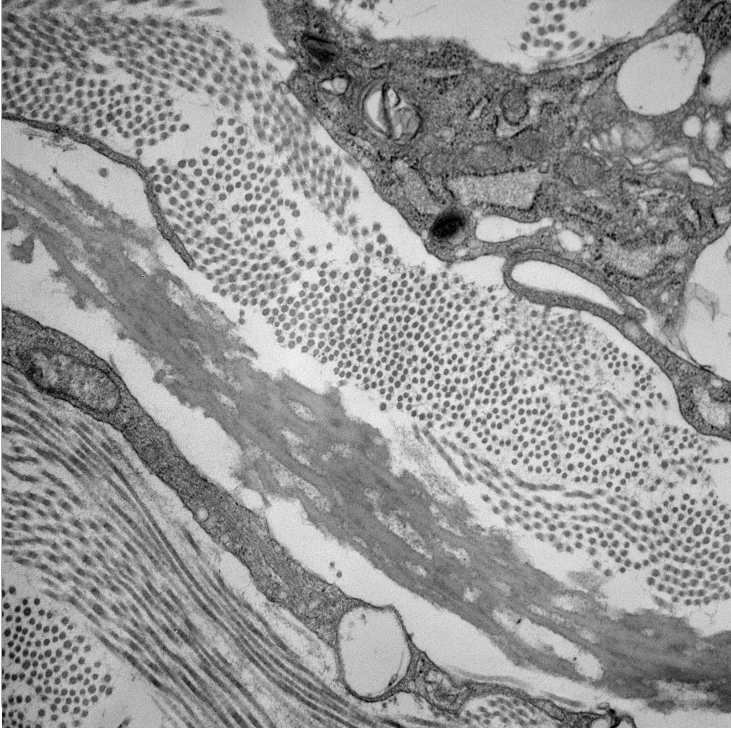
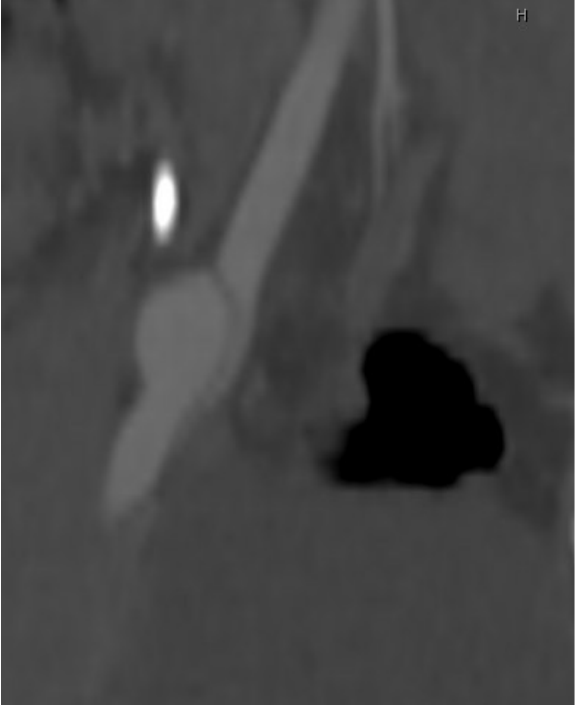
Control

Loeys-Dietz

VEDS



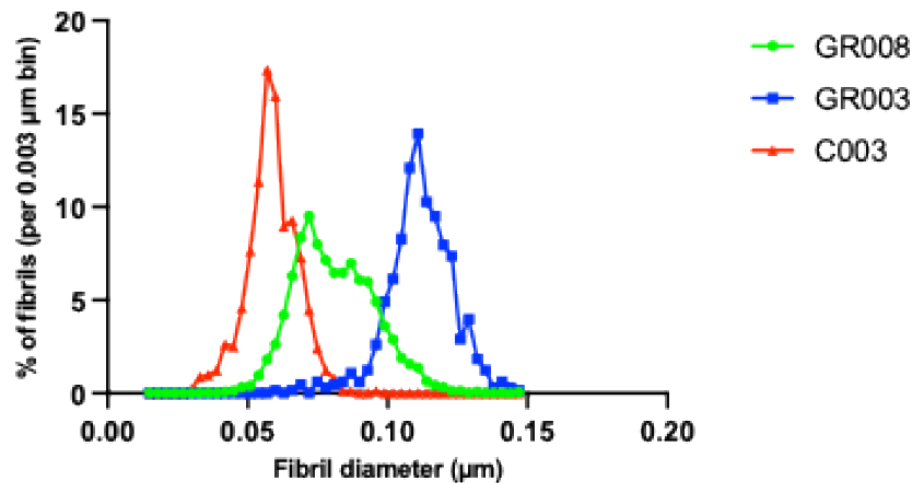
OHSU



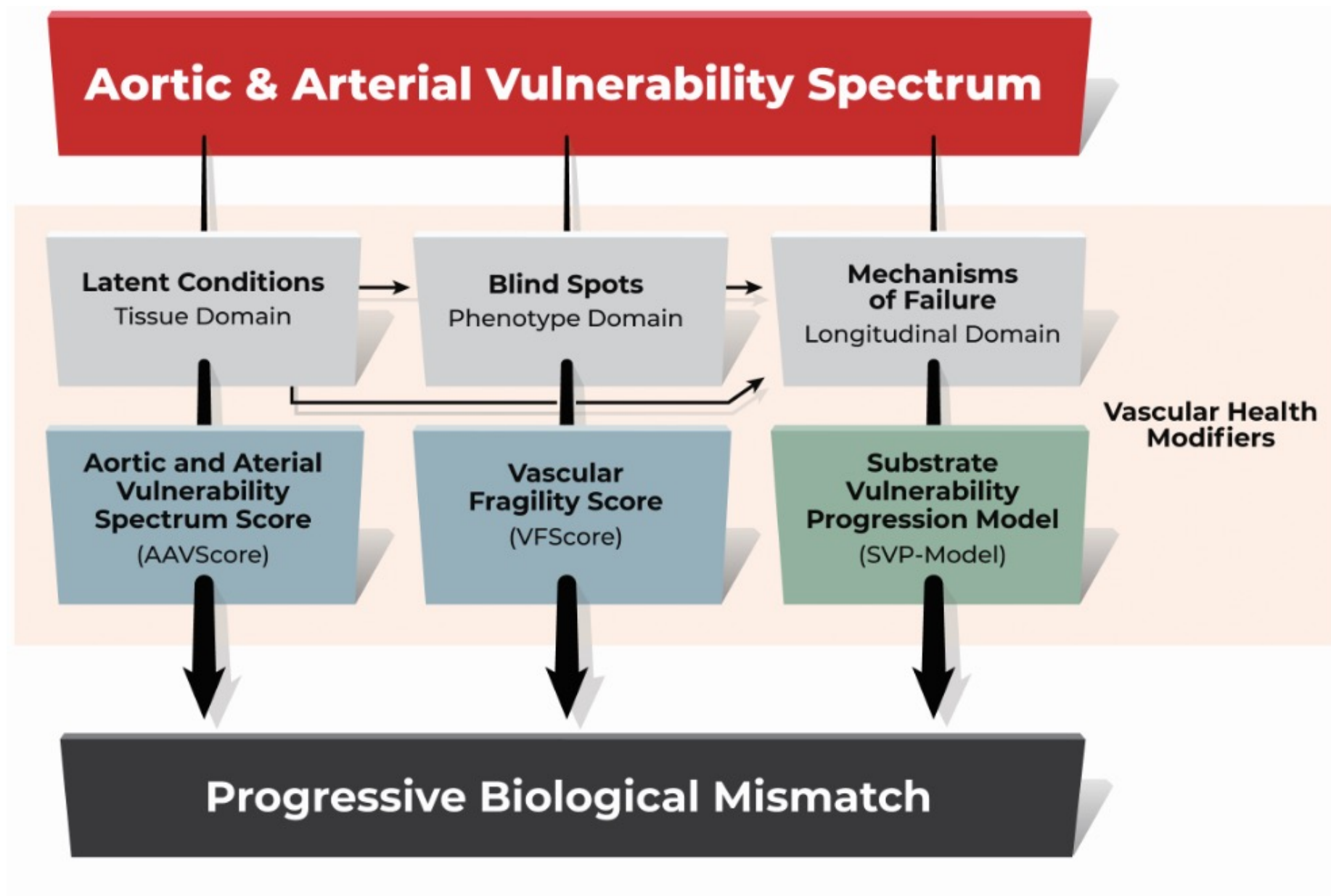
48-year-old
M w/ VEDS
COL3A1
c.852+1
G>A

26-year-old
M w/ VEDS
COL3A1
c.1347+1G>A

Frequency Distribution of Reticular Collagen Fibril Diameters — Relative frequency (%)



From
thresholds to
trajectories
a shift in
cognitive
strategy





Adventuresinlove4Andie



Multi-institutional collaborative: Genotype-surgical phenotype and vascular outcomes in this patient population

Genetic Aortopathy and VEDS Natural History Study (GEN-VEDSS)

Aortic Outcomes Research in Genetic Syndromes (AORTAGEN)

Vascular Genetics Biospecimen Consortium (VGBC)



longitudinal, natural history study of VEDS
Community-based enrollment
started in 2019

Expanded to
VEDS LIKE
CONDITIONS

Patients and families as Research Partners

- Help design the consent protocol
- Community participation
- Enrollment
 - Patients
 - loved ones who have died
 - children
- ed feedback on study

