Practical TAA Genetics for the Surgeon: Ten Tips

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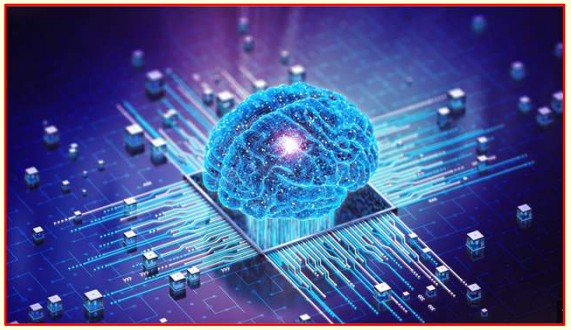
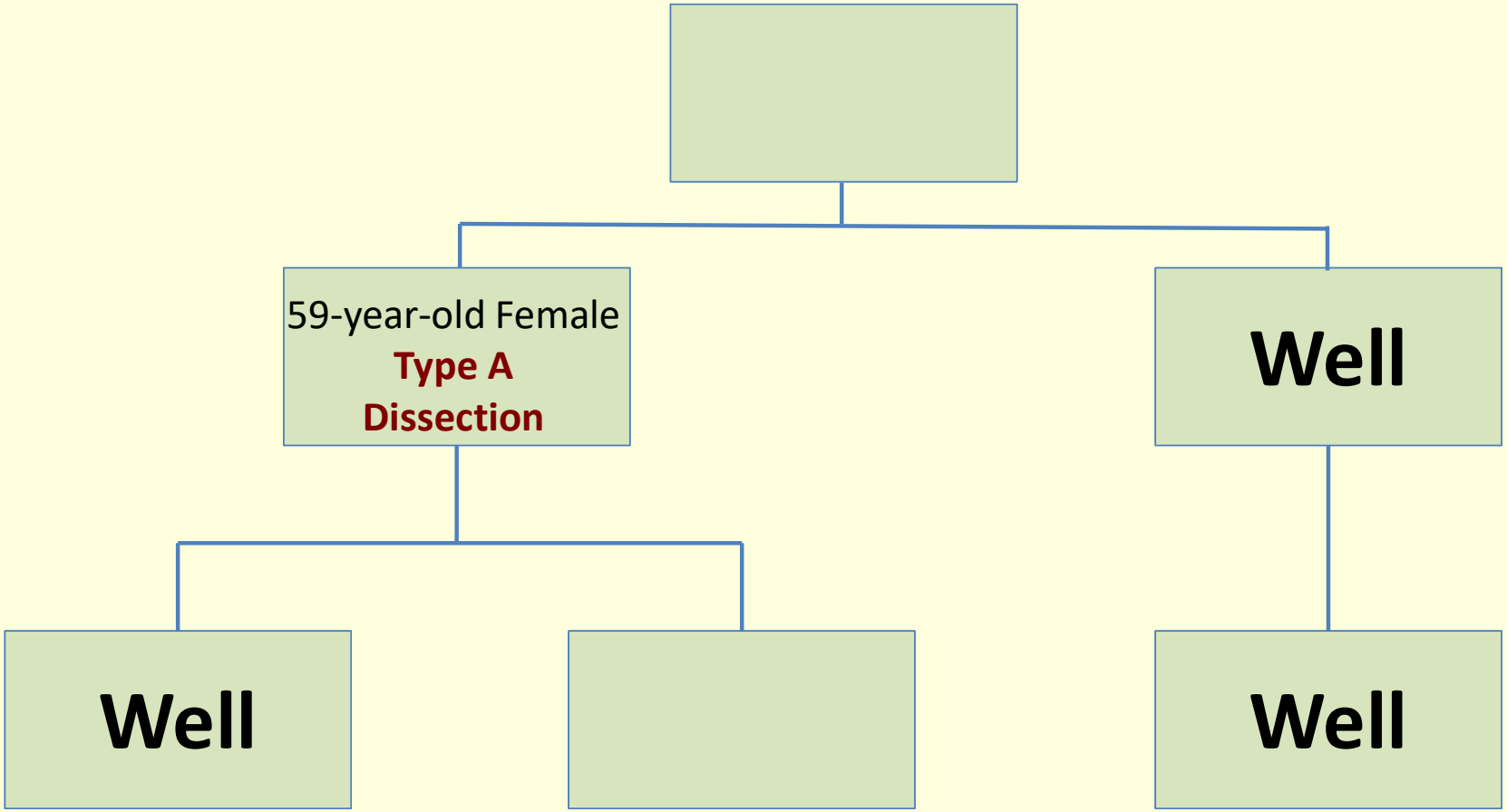
The Houston Aortic Symposium
Frontiers in Cardiovascular Diseases
The Eighteenth in the Series

March 5-7, 2026



Three Generations of Type A Dissection in One Single Family



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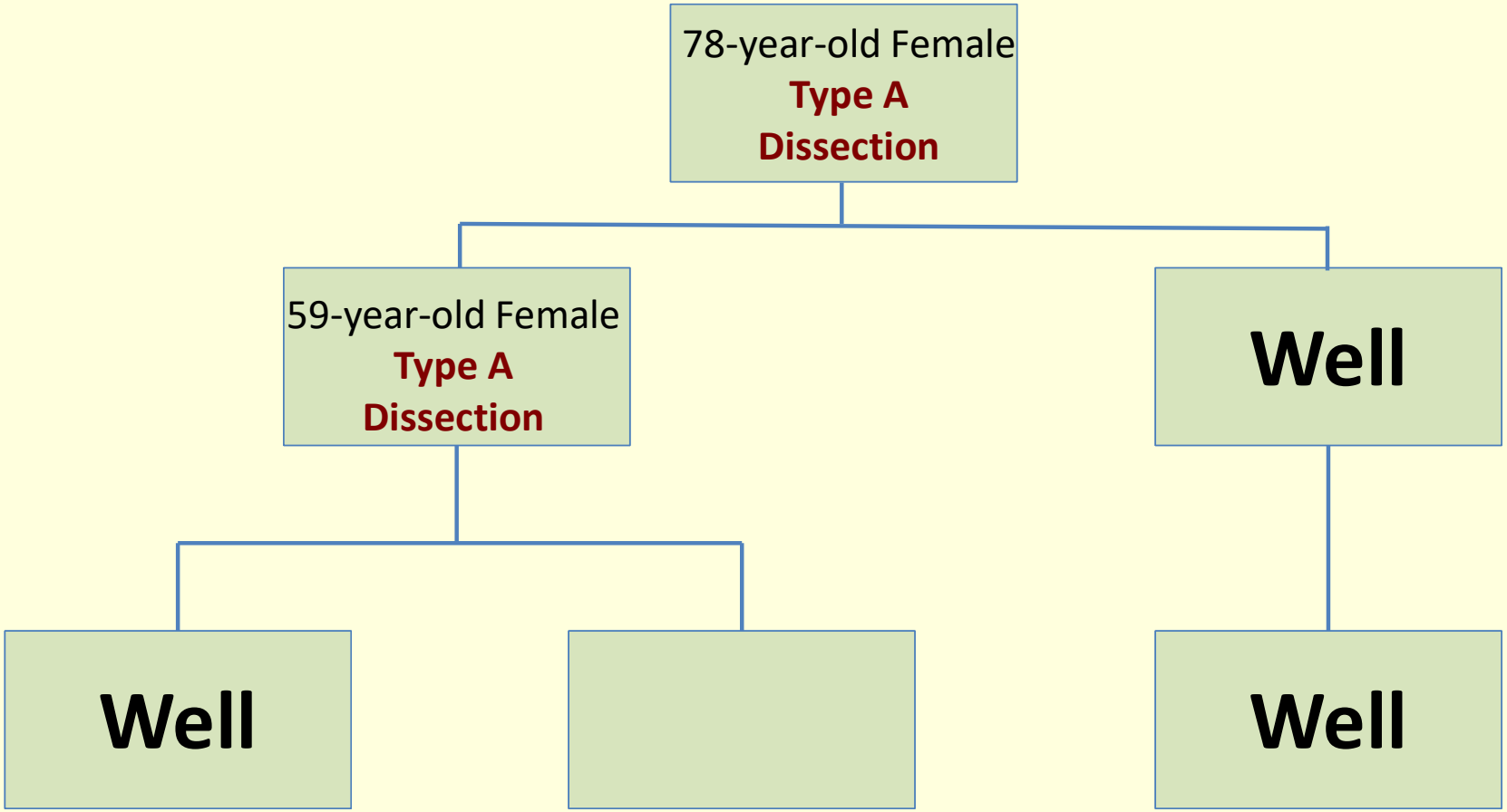

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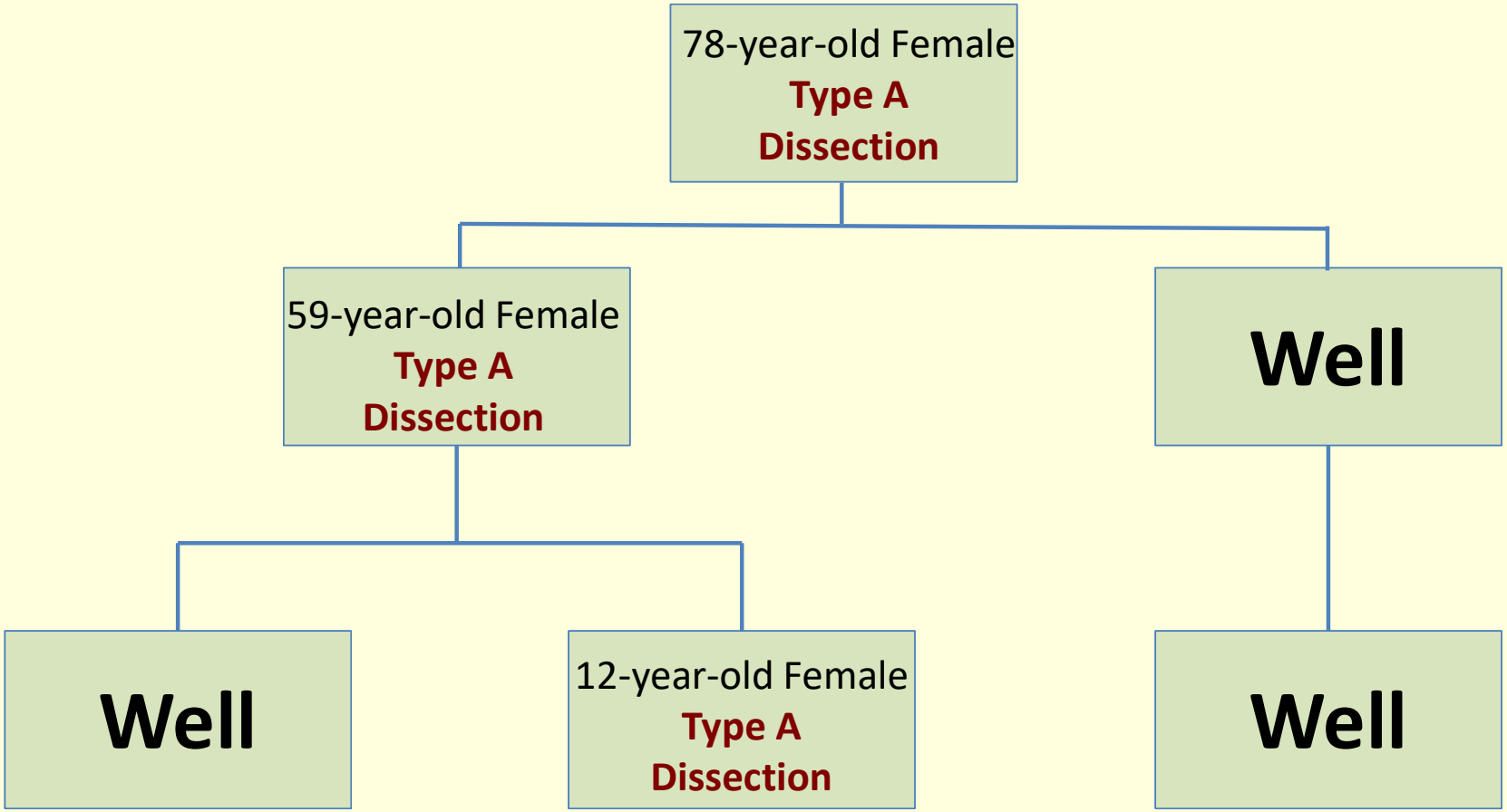
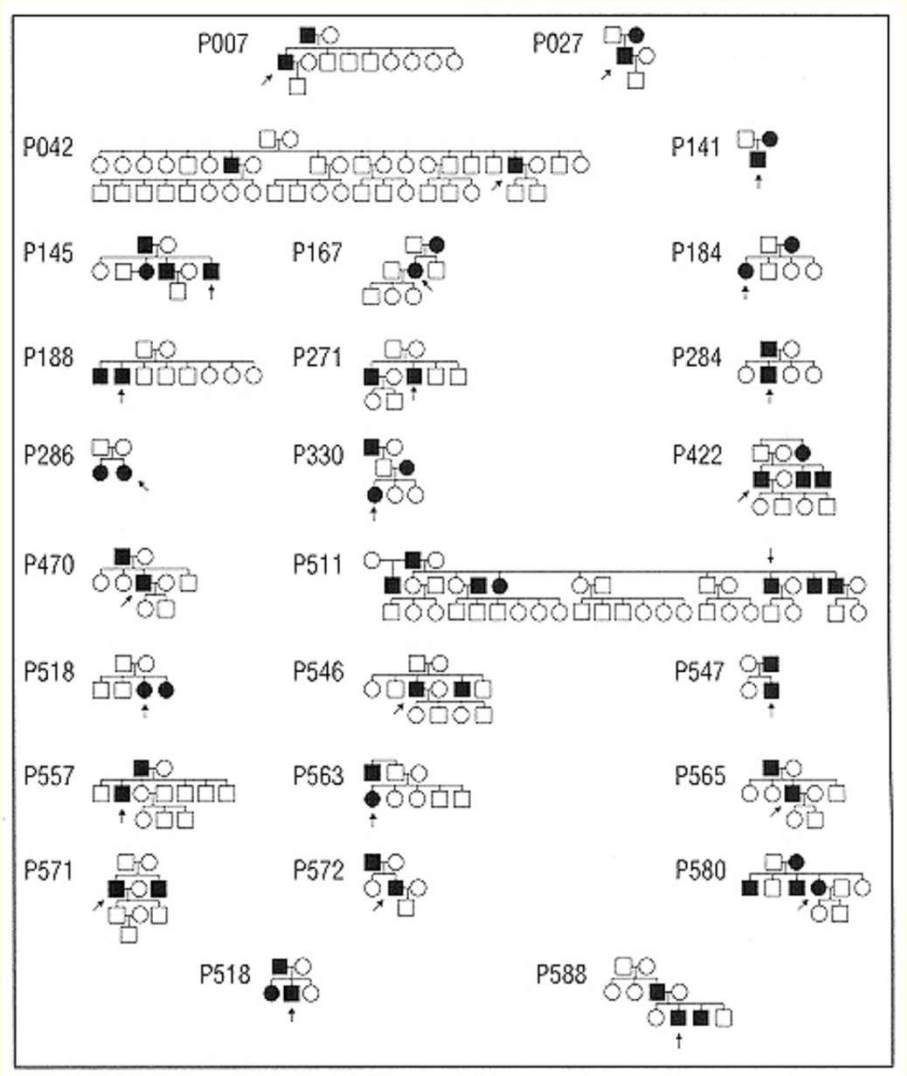




21% of TAA families manifest a genetic pattern of inheritance

PAPER

Familial Patterns of Thoracic Aortic Aneurysms

Michael A. Coady, MD, MPH; Ryan R. Davies, BA; Michele Roberts, MD, PhD; Lee J. Goldstein, BA; Matthew J. Rogalski, BS; John A. Rizzo, PhD; Graeme L. Hammond, MD; Gary S. Kopf, MD; John A. Elefteriades, MD

Hypothesis: To provide evidence that genetic factors contribute to the development of thoracic aortic aneurysms (TAA) by demonstrating familial patterns of the disease.

Design: Retrospective review.

Setting: University hospital.

Patients and Methods: We sought to identify familial patterns of TAA from a database of 598 patients evaluated or treated for TAA at the Yale Center for Thoracic Aortic Disease, New Haven, Conn, from January 1985 to August 1998. Of the 598 patients, 45 patients had a diagnosis of Marfan syndrome and 553 patients had no known history of any collagen vascular disorder. Of the 553 patients in the latter category, 398 patients had confirmed TAA, 66 had TAA with concomitant aortic dissections, and 89 had aortic dissections. From the group of 464 patients with TAA with or without concomitant aortic dissections, 2 interviewers attempted to contact 150 randomly selected patients for telephone screening to determine the presence of familial patterns of aortic disease. Fifteen of these patients were lost to follow-up. Complete medical and family histories of the remaining 135 patients (85 men, 50 women) were reviewed. Of the 135 individuals screened, 26 (18 men, 8 women) (19.3%) were found to belong to multiplex pedigrees. These 26 patients with familial nonsyndromic TAA were compared with the remaining 109 patients with sporadic TAA and the 45 patients with Marfan syndrome–associated TAA.

Main Outcome Measures: Groups were examined for statistical differences in age and aortic size at the time of diagnosis, growth rates of TAA, and rates of concomitant diseases. Nonsyndromic family pedigrees were analyzed and potential modes of inheritance were determined.

Results: The mean age at presentation for patients with familial nonsyndromic TAA (56.8 years) was significantly younger than the mean age of presentation in sporadic cases (64.3 years, $P \leq .03$), and significantly older than that of patients with Marfan syndrome (24.8 years, $P \leq .001$). Patients with a family history of aortic aneurysms had faster growth rates (0.22 cm/y) compared with patients with sporadic TAA (0.03 cm/y) ($P \leq .001$) and patients with Marfan syndrome (0.10 cm/y) ($P \leq .04$). Familial nonsyndromic TAA in patients with a concomitant aortic dissection had a growth rate of 0.33 cm/y, which was greater than that of patients with sporadic TAA (0.10 cm/y) and patients with Marfan syndrome (0.08 cm/y) with associated aortic dissection. This growth of 0.33 cm/y was significantly faster than the overall growth rate estimate of aneurysms in patients with aortic dissection (0.14 cm/y) ($P \leq .05$). Ten pedigrees (38.5%) showed direct father to son transmission, consistent with an autosomal dominant mode of inheritance. Six family pedigrees (23.1%) suggested an autosomal dominant or X-linked mode of inheritance. Seven pedigrees (26.9%) suggested a recessive mode of inheritance; 2 an autosomal recessive mode, and 5 an X-linked recessive or autosomal recessive mode. The remaining 3 pedigrees displayed more complex modes of inheritance.

Conclusions: This study supports the role of genetic factors influencing familial aggregation of TAA. Thoracic aortic aneurysms in association with multiplex pedigrees represent a new risk factor for aneurysm growth. Pedigree analysis suggests genetic heterogeneity. The primary mode of inheritance seems to be autosomal dominant, but X-linked dominant and recessive modes are also evident.

Arch Surg. 1999;134:361-367

1

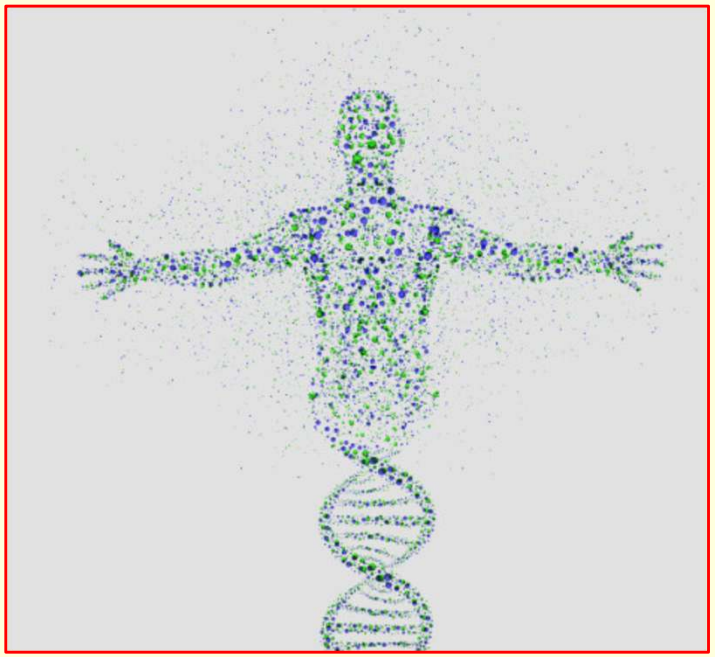
Thoracic aortic aneurysm is inherited in dominant hereditary fashion.

Classification	Chromosome	Gene	Protein	Location	Frequency	Inheritance
Syndromic:						
Marfan	15q21.1	FBN1	Fibrillin 1	ECM	1:5000-10,000	Dominant
Loeys-Dietz	3p24-25 9q33-34	TGFBR2, TGFBR1	TGFβ-R2 TGFβ-R1	Cell surface	Rare	Dominant
Ehlers-Danlos	2q24.3-31	COL3A1	Type III collagen	ECM	1:10,000-25,000	Dominant
ATS	20q13.1	SLC2A10	GLUT10	Intracellular	Rare	Recessive
AOS	15q22.2-24.3	SMAD3	SMAD3	Intracellular	Rare	Dominant
TGFβ2	1q41	TGFβ2	TGFβ2	Intracellular	Rare	Dominant
Cutis Laxa Syndrome	11q13.1	FBLN4	Fibulin-like	Extracellular	Rare	Recessive
Non-Syndromic:						
TAAD2	3p24-25	TGFBR2	TGFβ-R2	Cell surface	~3 % of TAA	Dominant
TAAD4	10q23-24	ACTA2	Actin	Intracellular	10-15% of TAA	Dominant
TAAD5	9q33-34	TGFBR1	TGFβ-R1	Cell surface	~2 % of TAA	Dominant
TAAD-PDA	16p12-13	MYH11	β-MHC	Intracellular	1-2% of TAA	Dominant
TAAD-PDA	3q21.1	MYLK	MLCK	Intracellular	~1% of TAA	Dominant

D. Milewicz

2

Thoracic aortic aneurysm (TAA) is a “single letter” disease.

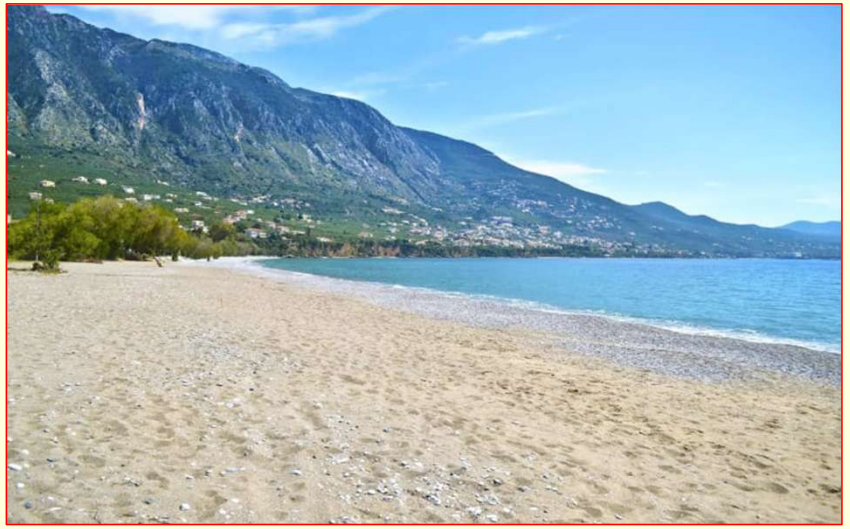


Thoracic Aortic Aneurysm is caused by a change in <u>just one letter!!</u>

Genome: 3.2 billion letters

Exome: 32 million letters

To cause TAA: 1 ‘bad’ letter



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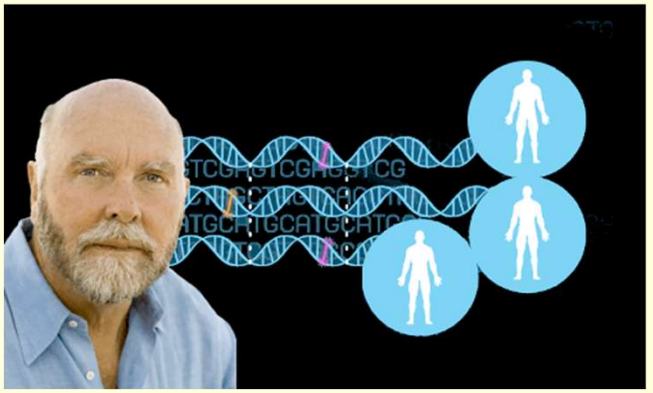
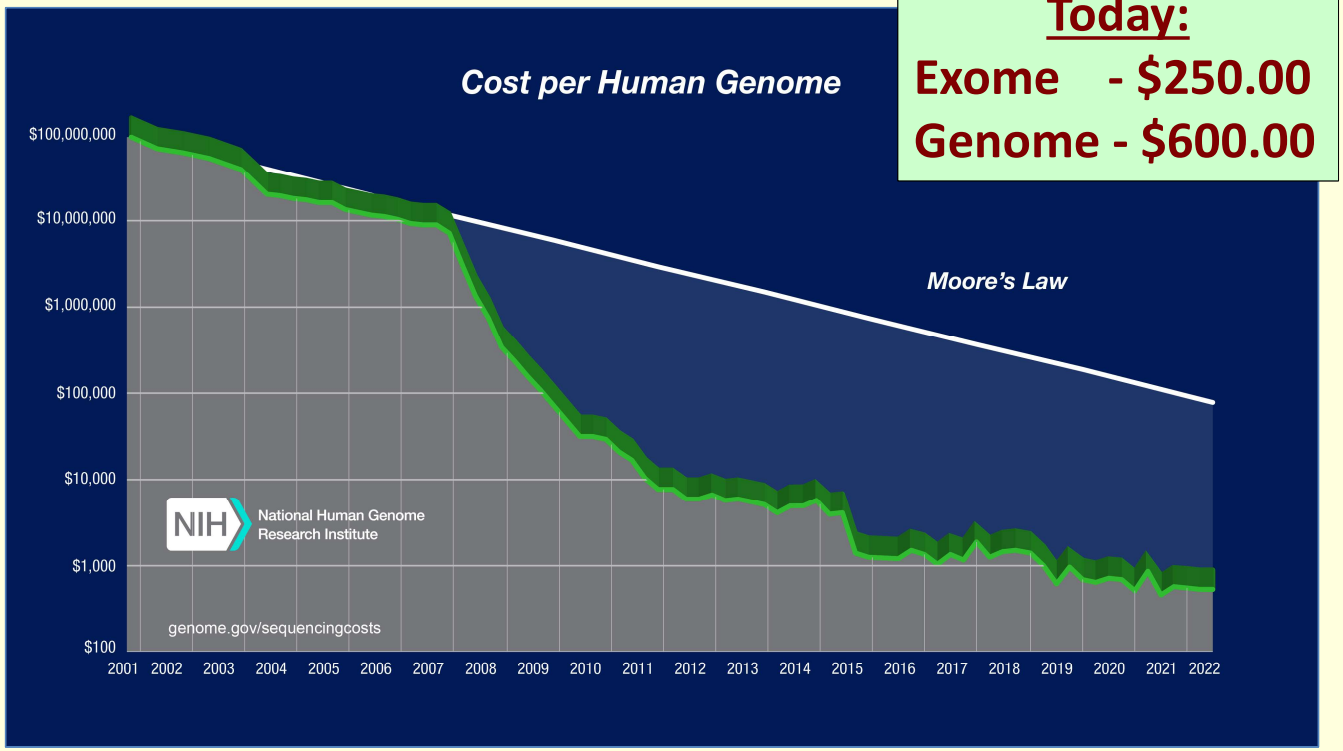
The cost of genetic sequencing is plummeting.



Today:
Exome - $250.00
Genome - $600.00

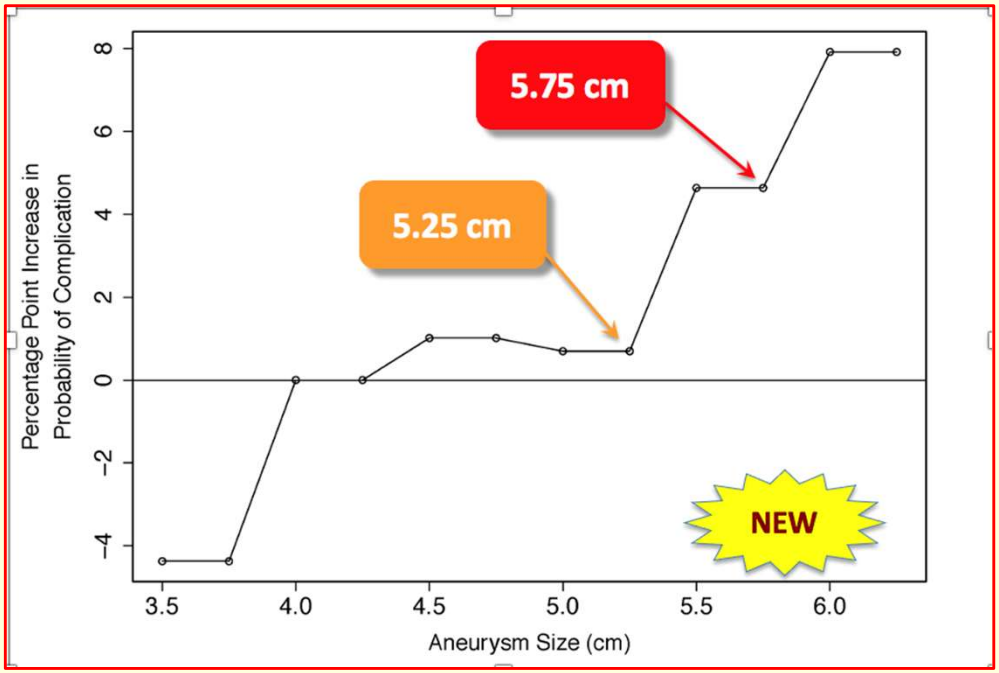


1. Shaer et al. Foundations and Trends® in Human-Computer Interaction · January 2017
2. https://www.famousscientists.org/craig-venter/

4

Whole Exome Genetic Sequencing permits individualized aortic care and decision making.

All patients treated similarly—one bucket for care.



4

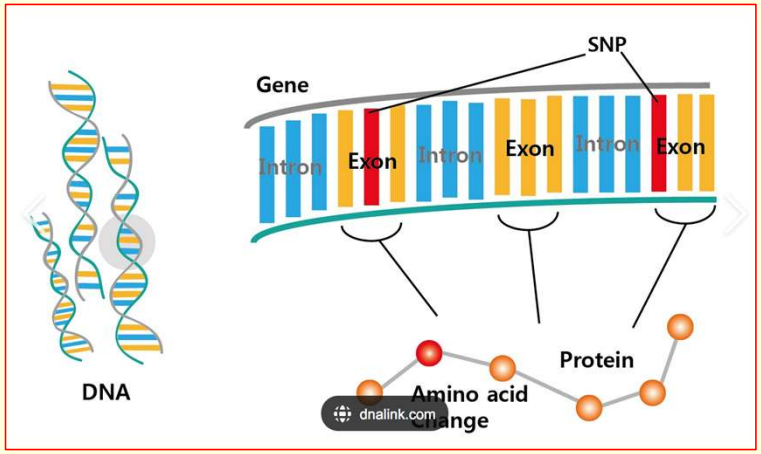
Whole Exome Genetic Sequencing permits individualized aortic care and decision making.

All patients treated similarly—one bucket for care.

ABCC6, ABL1, **ACTA2**, ACVR1, ADAMTS2, ADAMTSL4, ALDH18A1, ARIH1, ASPH, ATP6V0A2, ATP7A, B4GALT7, BGN, **CBS**, CHST14, COL11A1, COL11A2, COL1A1, COL1A2, COL2A1, **COL3A1**, COL4A1, **COL4A5**, COL5A1, COL9A1, COL9A2, COL9A3, **EFEMP2**, **ELN**, EMILIN1, **FBN1**, **FBN2**, FKB14, FLCN, **FLNA**, FOXE2, HEY2, HNRNPK, IPO8, KCNN1, **LOX**, LTB2, LTP3, MED12, MFAPS, **MHY11**, **MYLK**, MYLY2, **NOTCH1**, **PKD1**, **PKD2**, PLOD1, **PRKG1**, **SKI**, **SLCA2A10**, SLCA13, SMAD2, **SMAD3**, **SMAD4**, SMAD6, **TGFB2**, TGFB3, **TGFBR1**, **TGFBR2**, THSD4, TNXB, ZNF469.

ABC Definitive
ABC Strong
ABC Moderate
ABC Limited
ABC Without strong evidence to date

4



INDIVIDUALIZED CARE—GENE BASED

Etc. Etc.

Whole Exome Sequencing

MYH11

TGFB3

ACTA2

MYLK

……

5

We sequence everyone. Important, clinically actionable information therein resides.

ABCC6, ABL1, **ACTA2**, ACVR1, ADAMTS2, ADAMTSL4, ALDH18A1, ARIH1, ASPH, ATP6V0A2, ATP7A, B4GALT7, BGN, **CBS**, CHST14, COL11A1, COL11A2, COL1A1, COL1A2, COL2A1, **COL3A1**, COL4A1, **COL4A5**, COL5A1, COL9A1, COL9A2, COL9A3, **EFEMP2**, **ELN**, EMILIN1, **FBN1**, **FBN2**, FKB14, FLCN, **FLNA**, FOXE2, HEY2, HNRNPK, IPO8, KCNN1, **LOX**, LTB2, LTP3, MED12, MFAPS, **MHY11**, **MYLK**, MYLY2, **NOTCH1**, **PKD1**, **PKD2**, PLOD1, **PRKG1**, **SKI**, **SLCA2A10**, SLCA13, SMAD2, **SMAD3**, **SMAD4**, SMAD6, **TGFB2**, TGFB3, **TGFBR1**, **TGFBR2**, THSD4, TNXB, ZNF469.

To date, 71 genes have been identified that contribute to TAA disease.

- **Note different degrees of strength of association.**

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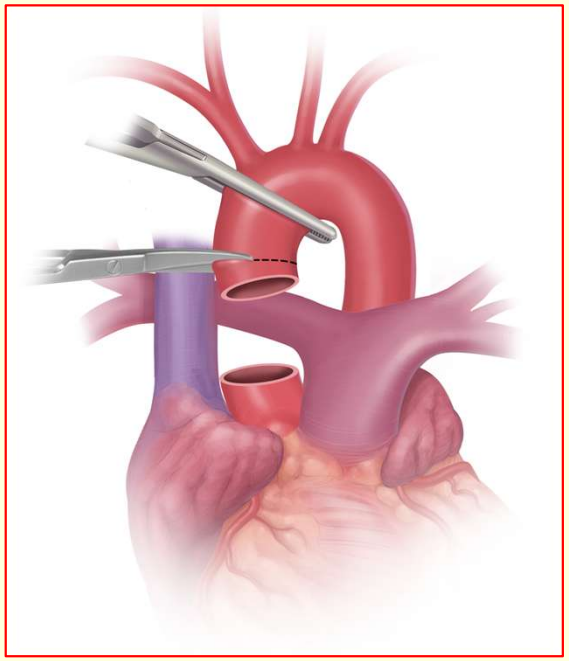
ABC Definitive
ABC Strong
ABC Moderate
ABC Limited
ABC Without strong evidence to date

6

Our team (with Dr. Chung at Columbia) has just identified *a new TAA causative gene*, based on advanced computerized analysis of 1753 of my excised human aortic tissue specimens.



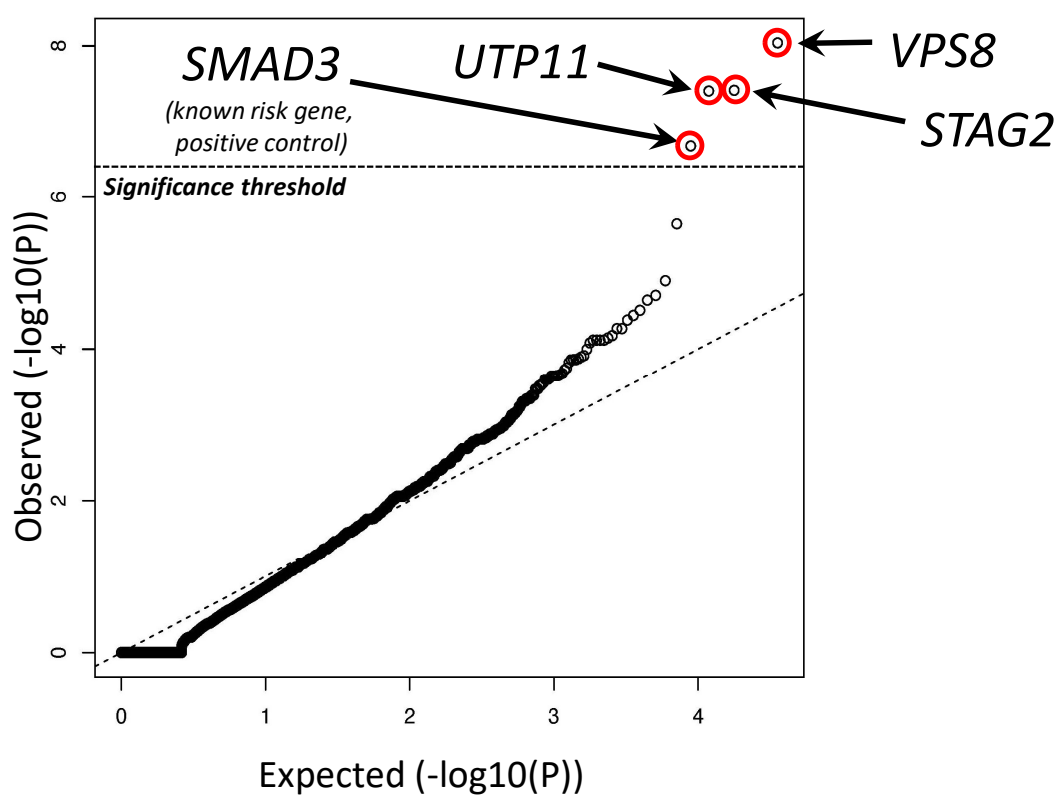
1) **VPS8**

VPS8 seems to be a very nasty gene—common, causing high-grade aortic dilatation, and behaving malignantly, with sudden dissection as the presenting modality.

Presented at the American Society of Human Genetics (ASHG) in Washington, DC, November 1-5, 2023.

6

Dr. Ziganshin from our team (with Dr. Chung at Columbia) has just identified *3 new TAA causative genes*, based on advanced computerized analysis of 1753 of my excised human aortic tissue specimens.



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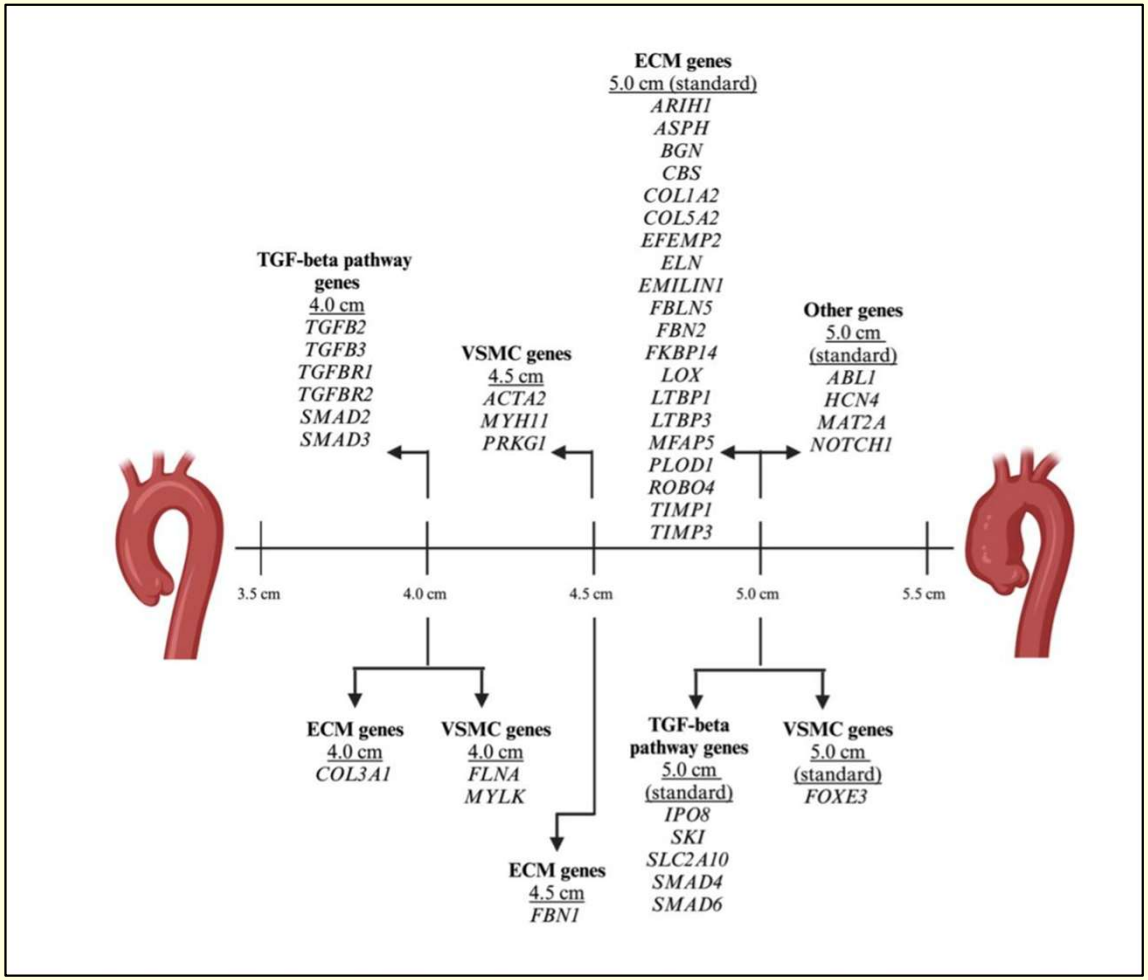
7

Use the **"Sizeline"** to gauge appropriate time for surgical intervention.



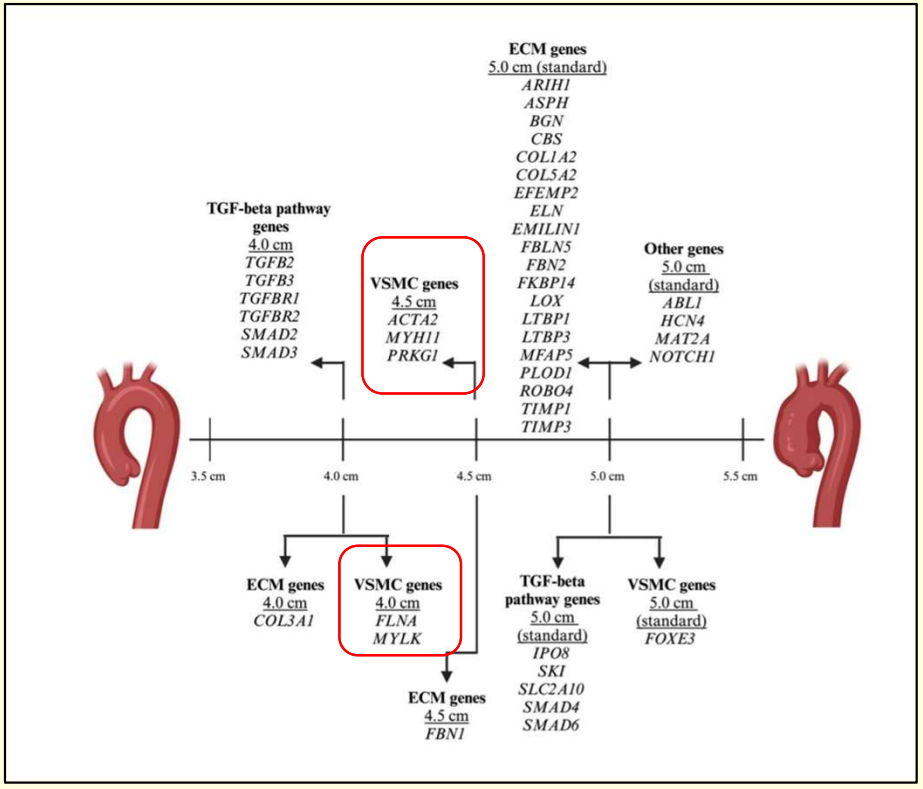
Updated every 2 years in the journal *AORTA*.

8

Remember two common genes that behave badly:

- Smooth muscle contractile genes
- ACTA 2 can dissect at < 5 cm
- MYLK can dissect without aortic enlargement.

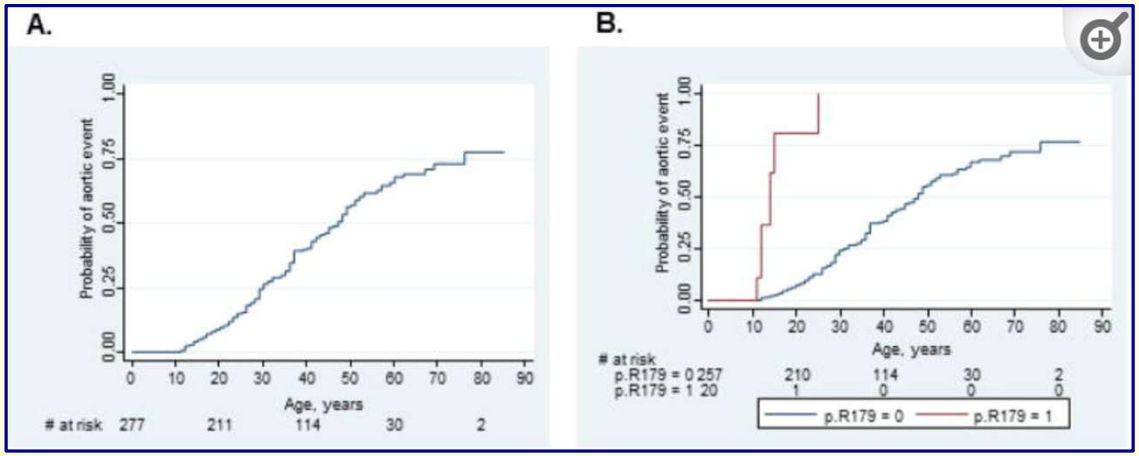
ACTA2

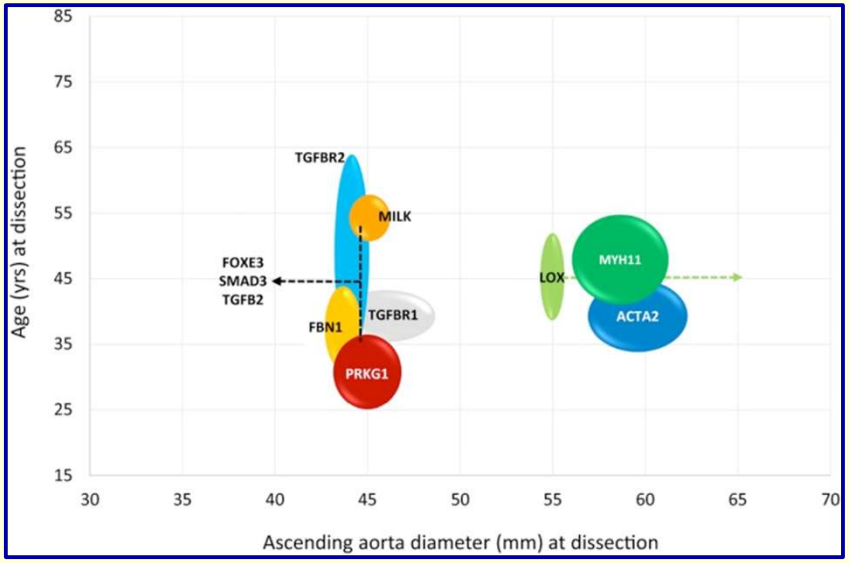


MYLK

9

Remember that **age plays a gene-specific role**, in addition to diameter.





1. Regalado ES, Milewicz D et al. Circ Cardiovasc Gen. 2015
2. Mariscalco G, Elefteriades, et al. JAHA. 2018.

10

Report of DNA Analysis

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MR xxxxxxxxxx

testing should be used in line with other clinical information when possible.
LIKELY PATHOGENIC: Sufficient information exists to justify using the genetic test in clinical decision making when combined with other evidence for the disease in question (e.g., supporting biochemical studies, imaging studies, or clinical findings).
VARIANT OF UNCERTAIN SIGNIFICANCE: Variant for which current evidence is insufficient to determine pathogenicity. A substantial portions of variants of uncertain significance prove to be benign as more data become available. A VARIANT OF UNCERTAIN SIGNIFICANCE SHOULD NOT BE USED IN CLINICAL DECISION MAKING. Efforts to classify the variant as pathogenic or benign should be undertaken.
NO VARIANTS REPORTED: No differences from the standard human genome reference sequence were found, or only genetic variants known to be benign polymorphisms were found, or only silent variants or deep intronic variants not known to affect gene function were found._____
LIMITATIONS: It is possible that this patient has a variant not detected by the methodology used. This study would not have detected large scale inversions, balanced translocations, or trinucleotide repeat expansions and would not

ACMG CRITERIA: Benign or Disease-causing

- Rarity in the general population (not rare—>not the cause of a relatively rare disease)
- Impact on reading of the genome (affects codon, missence, non-sense, stop codon?)
- Preservation in phylogeny
- Clinical segregation of genotype with phenotype (**Generations!**)

ACMG Guidelines for Variant (VUS) Classification

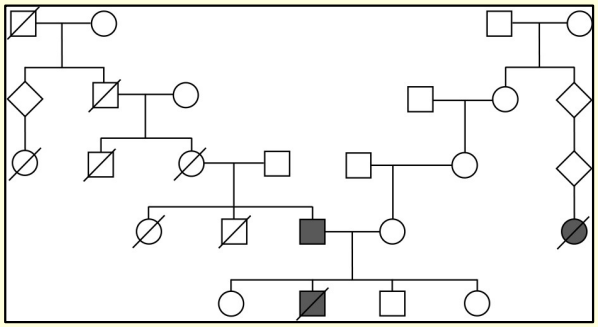
SEVERITY

- Benign
- Likely benign
- Uncertain significance
- Likely pathogenic
- Pathogenic

Pedigree Analysis May Be Complex and Take Generations

May take not hours or days or weeks or months or years, but *generations* to confirm co-segregation.

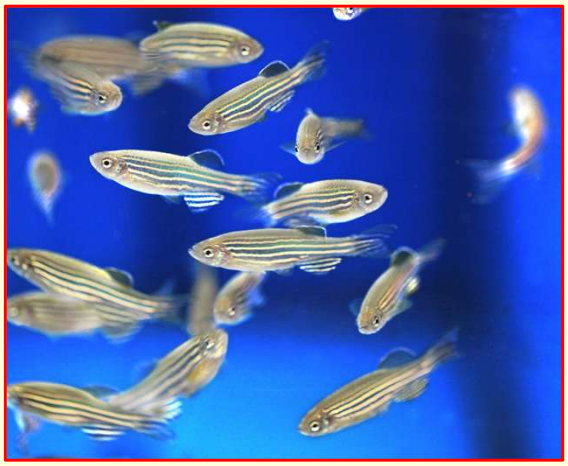
The surgeon is fearful that the patient may succumb during this time.



A MORE RAPID SOLUTION TO THE "VARIANT OF UNCERTAIN SIGNIFICANCE" (VUS) IS NEEDED!

10

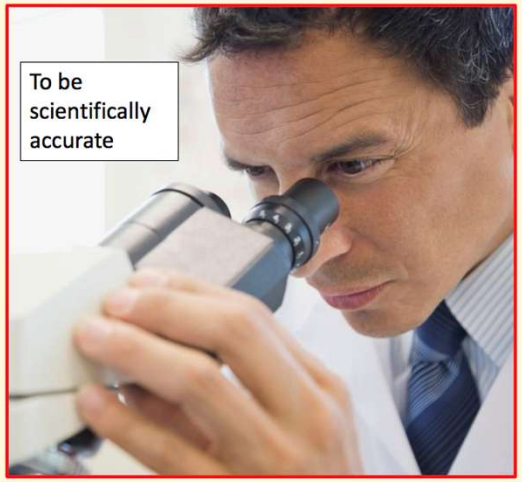
The zebrafish model may help us resolve issues of significance of genetic variance in real time, without waiting for generations.



GENETICIST

SURGEON

DIFFERENT PERSPECTIVES AND GOALS



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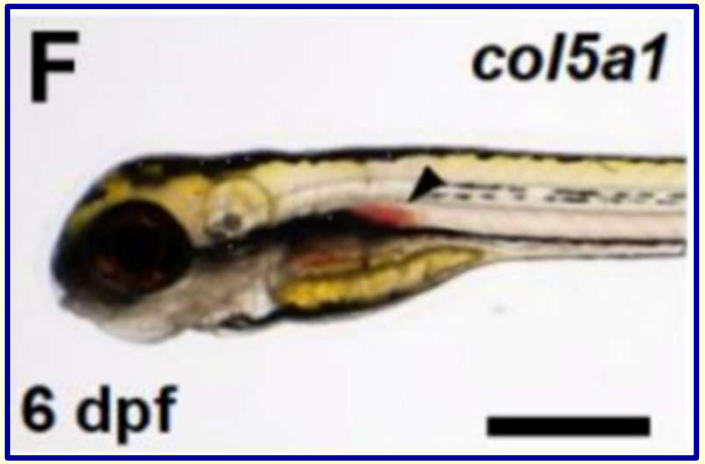
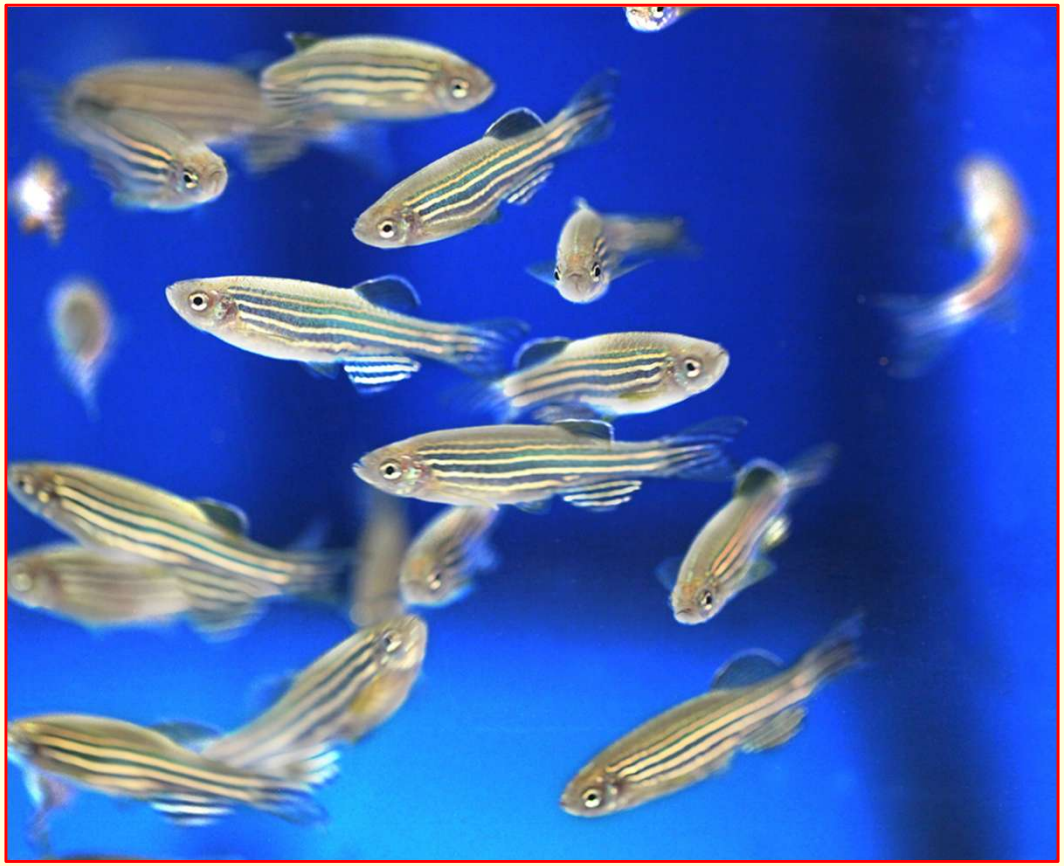
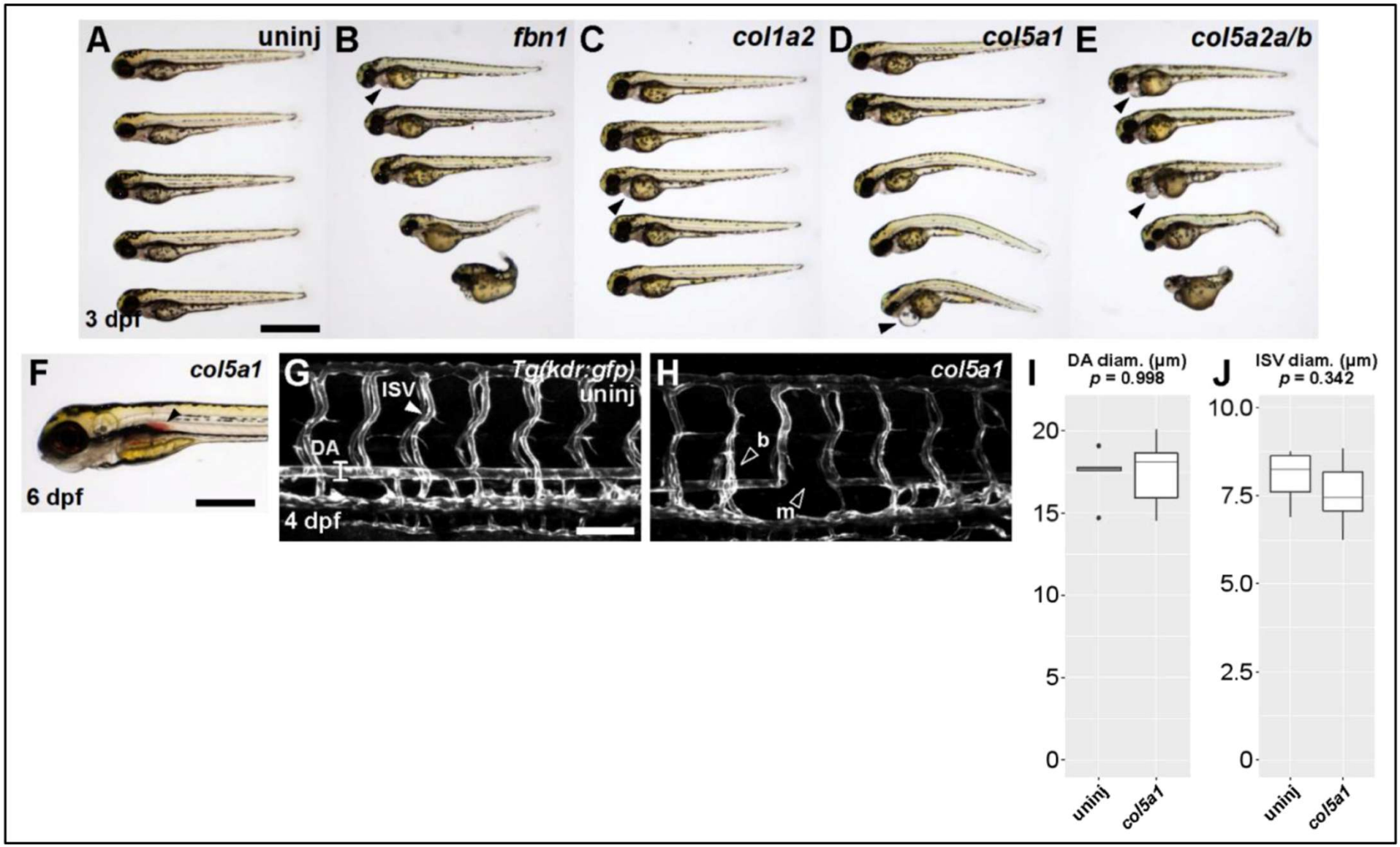
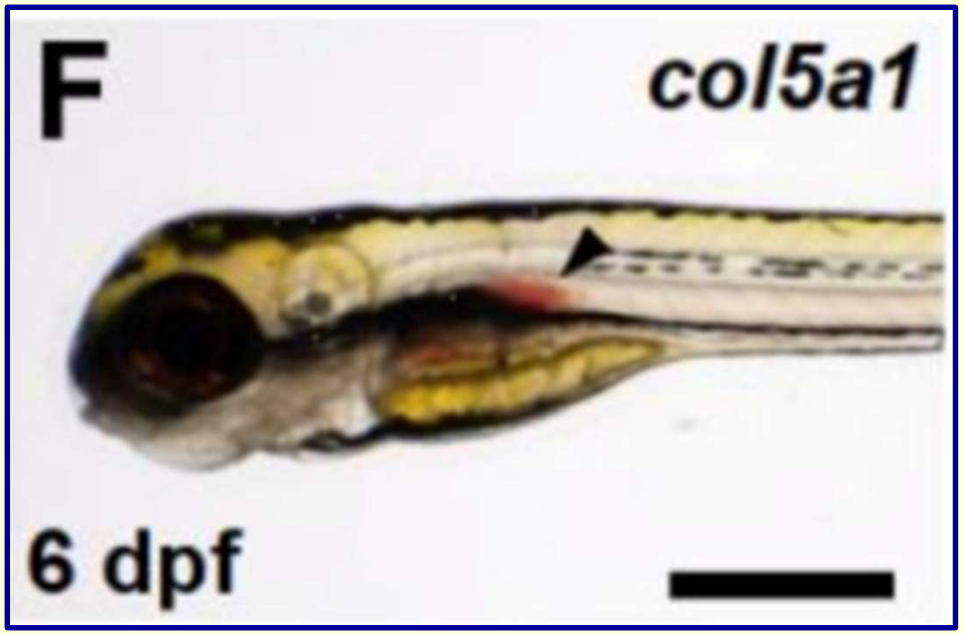


Yale Thoracic Aortic Aneurysm Zebrafish Project




A
uninj
B
fbn1
C
col1a2
D
col5a1
E
col5a2a/b
3 dpf
F
col5a1
6 dpf
G
Tg(kdr:gfp)
uninj
ISV
DA
4 dpf
H
col5a1
b
m
I
DA diam. (μm)
p = 0.998
20
15
10
5
0
uninj
col5a1
J
ISV diam. (μm)
p = 0.342
10.0
7.5
5.0
2.5
0
uninj
col5a1

Brain hemorrhage



Dorsal aortic hemorrhage

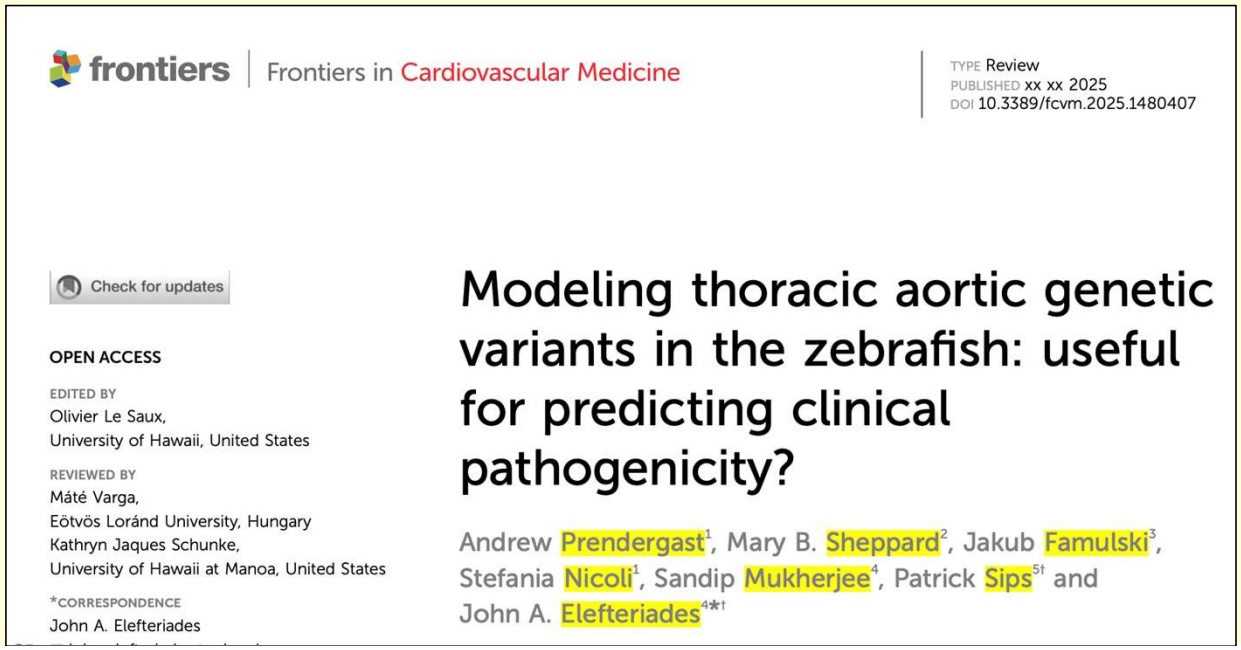
genes

MDPI

Article

Phenotyping Zebrafish Mutant Models to Assess Candidate Genes Associated with Aortic Aneurysm

Andrew Prendergast [1], Bulat A. Ziganshin [2], Dimitra Papanikolaou [2], Mohammad A. Zafar [2], Stefania Nicoli [1,3], Sandip Mukherjee [2] and John A. Elefteriades [2,*]



frontiers | Frontiers in Cardiovascular Medicine

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Modeling thoracic aortic genetic variants in the zebrafish: useful for predicting clinical pathogenicity?

Andrew Prendergast[1], Mary B. Sheppard[2], Jakub Famulski[3], Stefania Nicoli[1], Sandip Mukherjee[4], Patrick Sips[5†] and John A. Elefteriades[4*†]

What is the accuracy of Zebrafish testing in determining the true pathogenicity of aortic genetic variants?

Hot Off the Press!!

P = 0.01

Pathogenic

Non-Pathogenic

EJ1

Future

<u>The future is here</u>: We can curtail the scourge of genetic diseases causing TAA and dissection: via *IVF* Selection and soon, *gene editing*.

With IVF, there is no reason for offspring to be born harboring a TAA gene. We can diminish this disease in the human population by selecting unaffected embryos.

CRISPR is entering human application. We may soon be able to correct the single aberrant letter among the 3.2 billion in our genome to eliminate TAA disease.

https://r.search.yahoo.com/_ylt=AwrijcZE_vllUswskIyWnIlQ;_ylu=c2VjA2ZwLWF0dHJpYgRzbGsDcnVybA--/RV=2/RE=1710911172/RO=11/RU=https%3a%2f%2fwww.artfertilityclinics.com%2fin%2fen%2fart-blog%2fdifference-between-iui-and-ivf/RK=2/RS=Ip07s1l3BLfVlkwJZmtHGowQZuo-

Slide 29

EJ1 Elefteriades, John, 3/19/2024

- Adding together all known causes of TAA only explains 21% of clinical cases.
- What causes the remainder of the cases, and how do we identify those causes?