Blood Test for Thoracic Aortic Aneurysm

2nd International Meeting on Aortic Diseases
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Non-Size Indications for Aortic Replacement

1. Symptoms
2. Family Histor
3. (Mechanical properties)
4. (Biomarkers)

Aneurysms Largely Asymptomatic

- Vast majority of patients with TAA (90-95%) have no sx until rupture/dissection occur.[1,2]
- First symptom is usually death from rupture or dissection.
- Urgent need for screening tests.

1. Barrat-Boyes BG. Lancet 1957:716-720.
2. Elefteriades JA et al. Diseases of the Aorta. Hurst's The Heart. McGraw-Hill. New York. 2008.

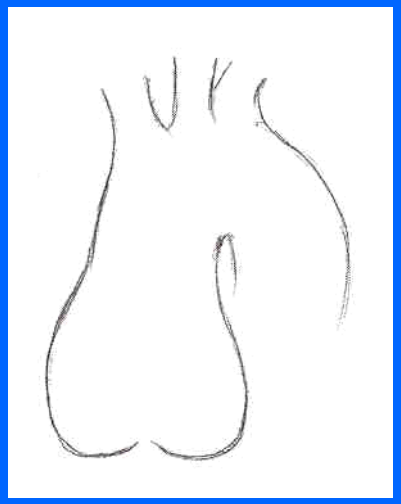
Healthy young men with only moderately enlarged aortas-> Aortic dissection while weightlifting

Elefteriades JA, et al. *JAMA.* Dec 5, 2003.

Why does dissection pick one point in time to occur?

MMPs

Genetic Predisposition



Exertion or emotion

Aortic Dilatation

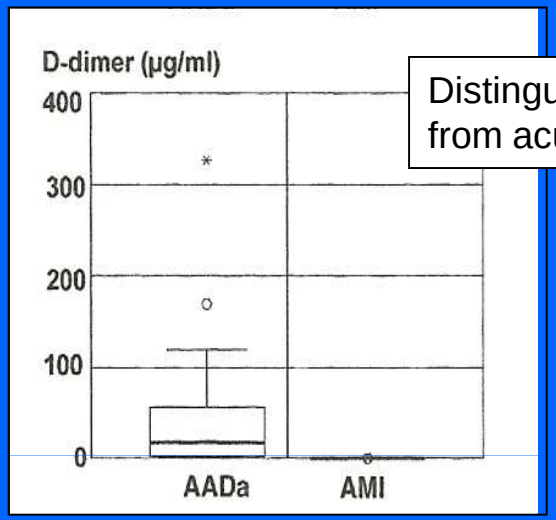
Blood Pressure

Acute Aortic Dissection

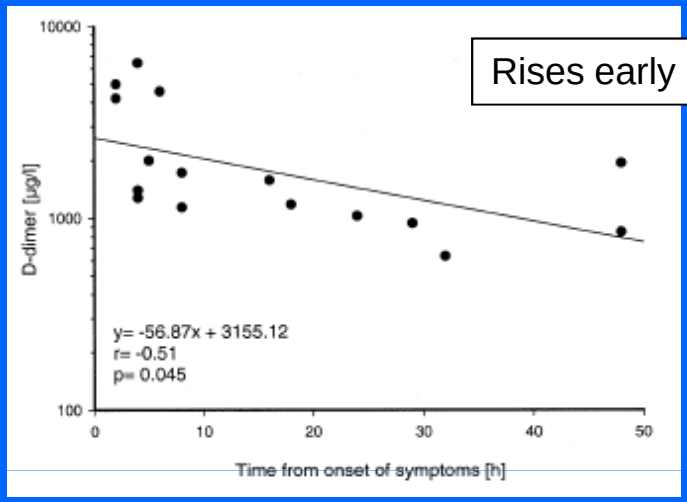
5. Biomarkers

- D-Dimer
- Markers of inflammation
  - CRP
  - CD4+CD28- T-Cells
- Matrix metalloproteinases
- Markers of collagen turn-over
  - Elastin Peptide (EP)
- Genetic markers
  - “RNA Signature”

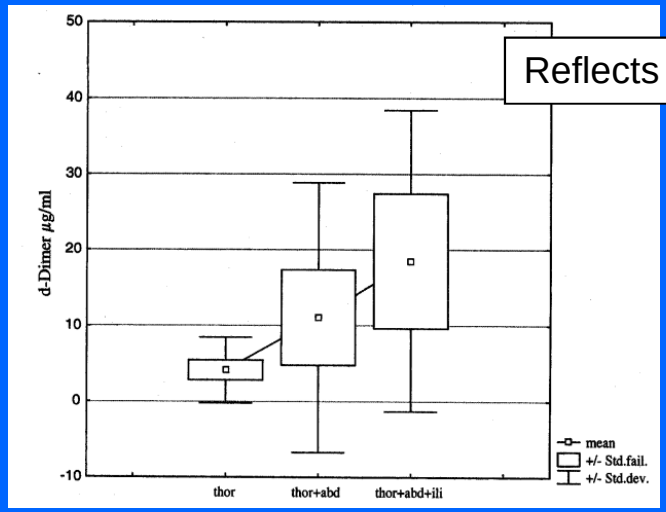
D-Dimer in Aortic Dissection-1



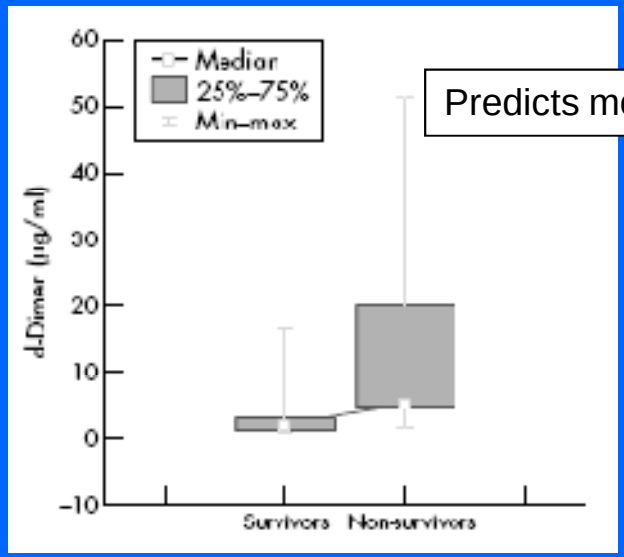
Distinguishes from acute MI



Rises early



Reflects extent



Predicts mortality

1. Hazui H et al. Circ J 2005;69:677-682.

2. Weber T et al. Chest 2003;123:1375-1378.

3. Eggebrecht H et al. J Am Coll Cardiol 2004;44:804-9

4. Weber T et al. Heart 2006;92:836-837.

TIMELINE

Matrix metalloproteinases: a tail of a frog that became a prince

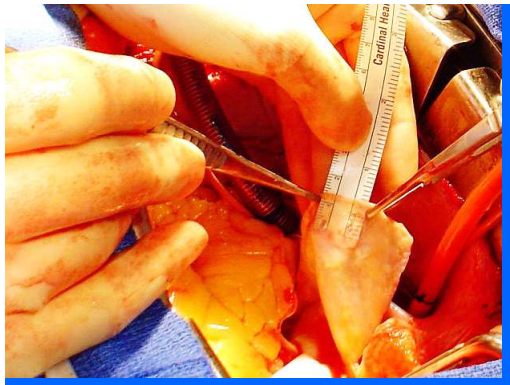
Constance E. Brinckerhoff and Lynn M. Matrisian

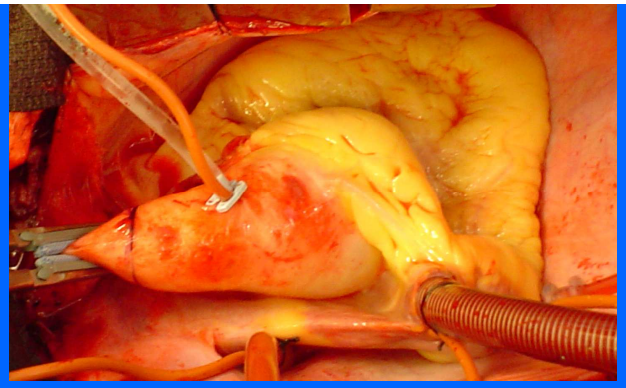
It is 40 years since the first member of what came to be known as the matrix metalloproteinase (MMP) family was described. Structural, molecular and biochemical approaches have subsequently contributed to piecing together the puzzle of how MMPs work, and how they contribute to various disease processes.

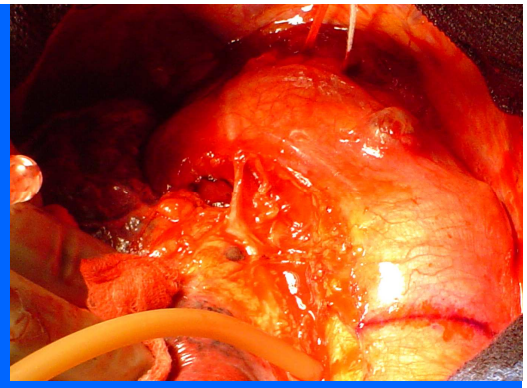
characterizing various activities. Nonetheless, over the years, there have been several landmarks (see TIMELINE) and, by 1989, the field had grown sufficiently to attract more than 250 people to an international MMP conference in Destin, Florida. This meeting was a forum for the introduction of the term 'matrix metalloproteinases' and for their numerical designation[6]. In addition, the

purified the enzyme from human skin[7] and then from the involuting rat uterus[8,9]. These studies must have seemed particularly daunting, as the investigators were unaware that the enzyme is synthesized and secreted in a latent form[10], and also that it could be activated by other proteases (and even, on occasion, by itself) during the process of purification[11]. Perhaps this was because tissues that contained high levels of collagenase also contained high levels of other enzymes that can activate latent collagenase, thereby camouflaging the 'real' state of the enzyme.

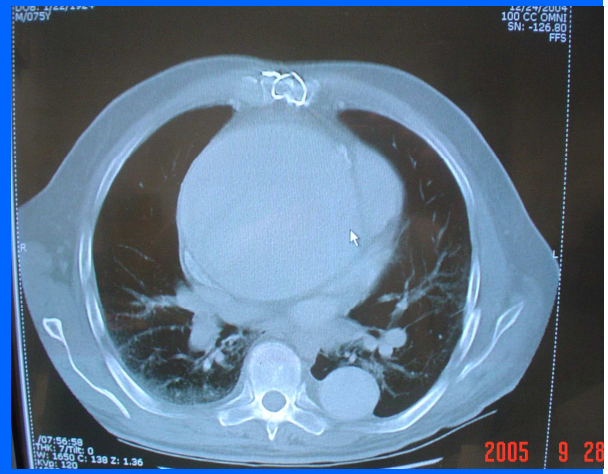
Subsequent advances in the purification of homogeneous enzymes were aided by the discovery that isolated cells in tissue culture produce copious amounts of MMPs in a latent form. As the zymogen nature of collagenase became clear, investigations that

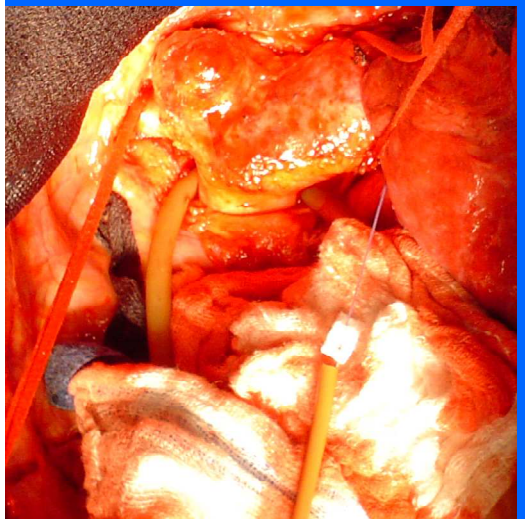


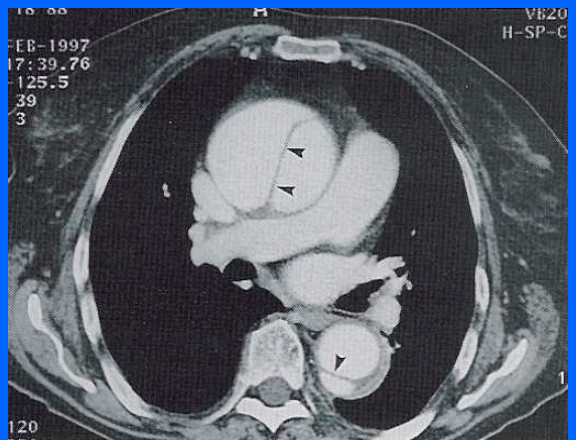


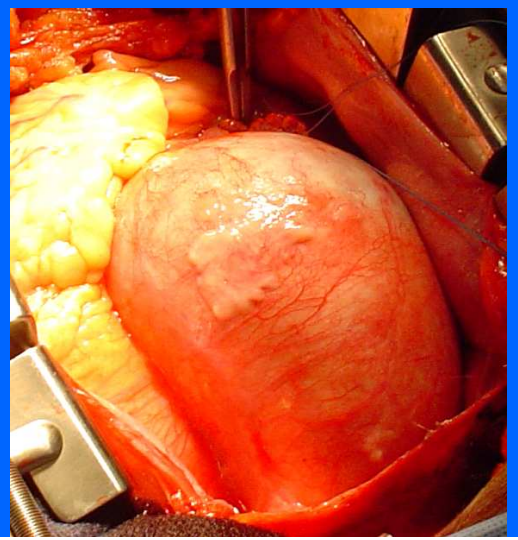


- Research at Yale and other programs indicates an important etiologic role for excess MMP activity in the destruction of the aortic wall underlying thoracic aortic aneurysm disease.

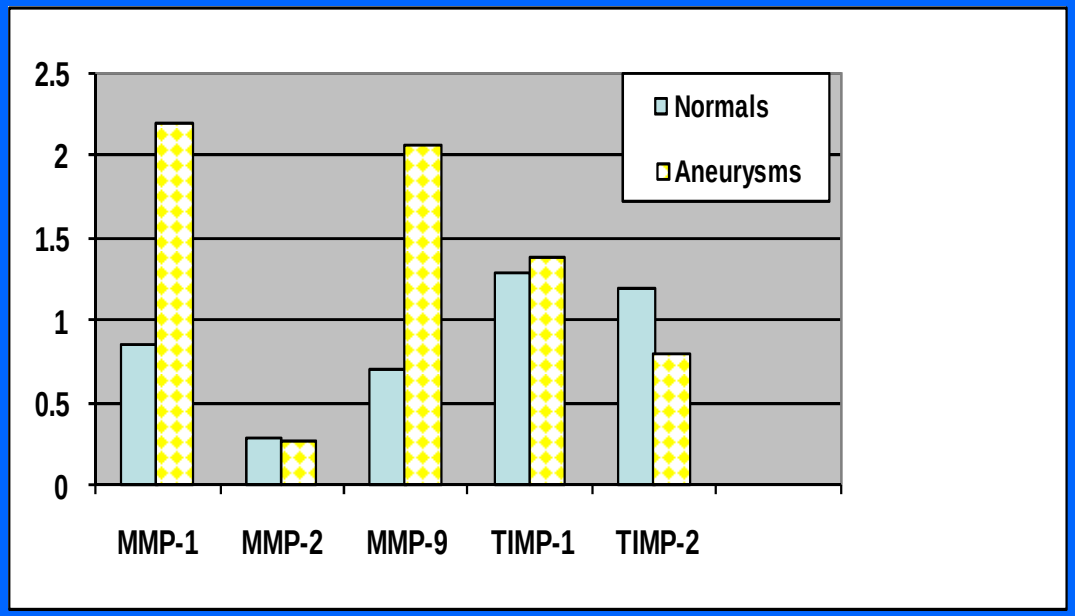


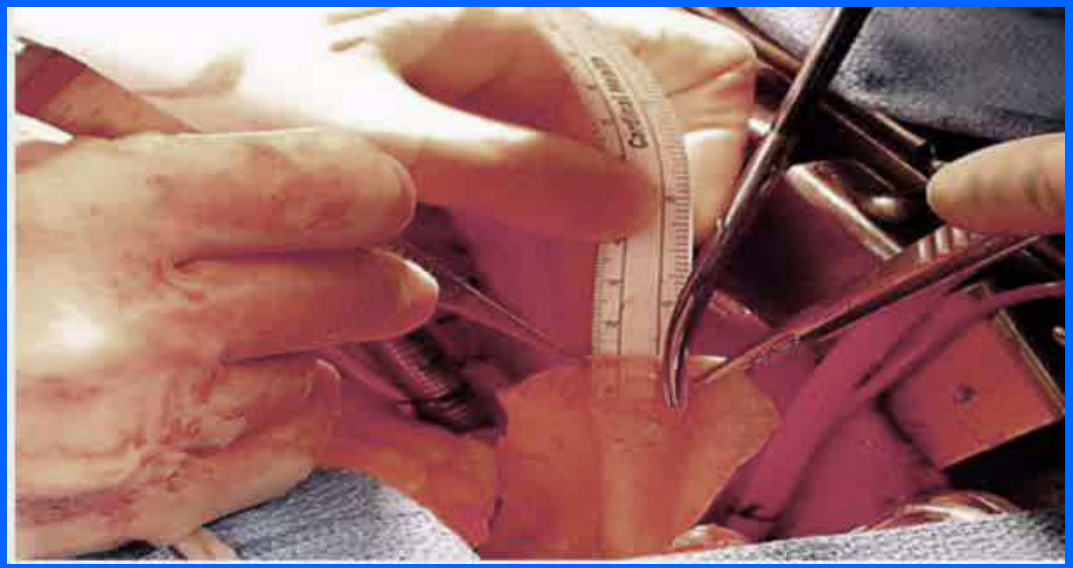






MMP Analysis





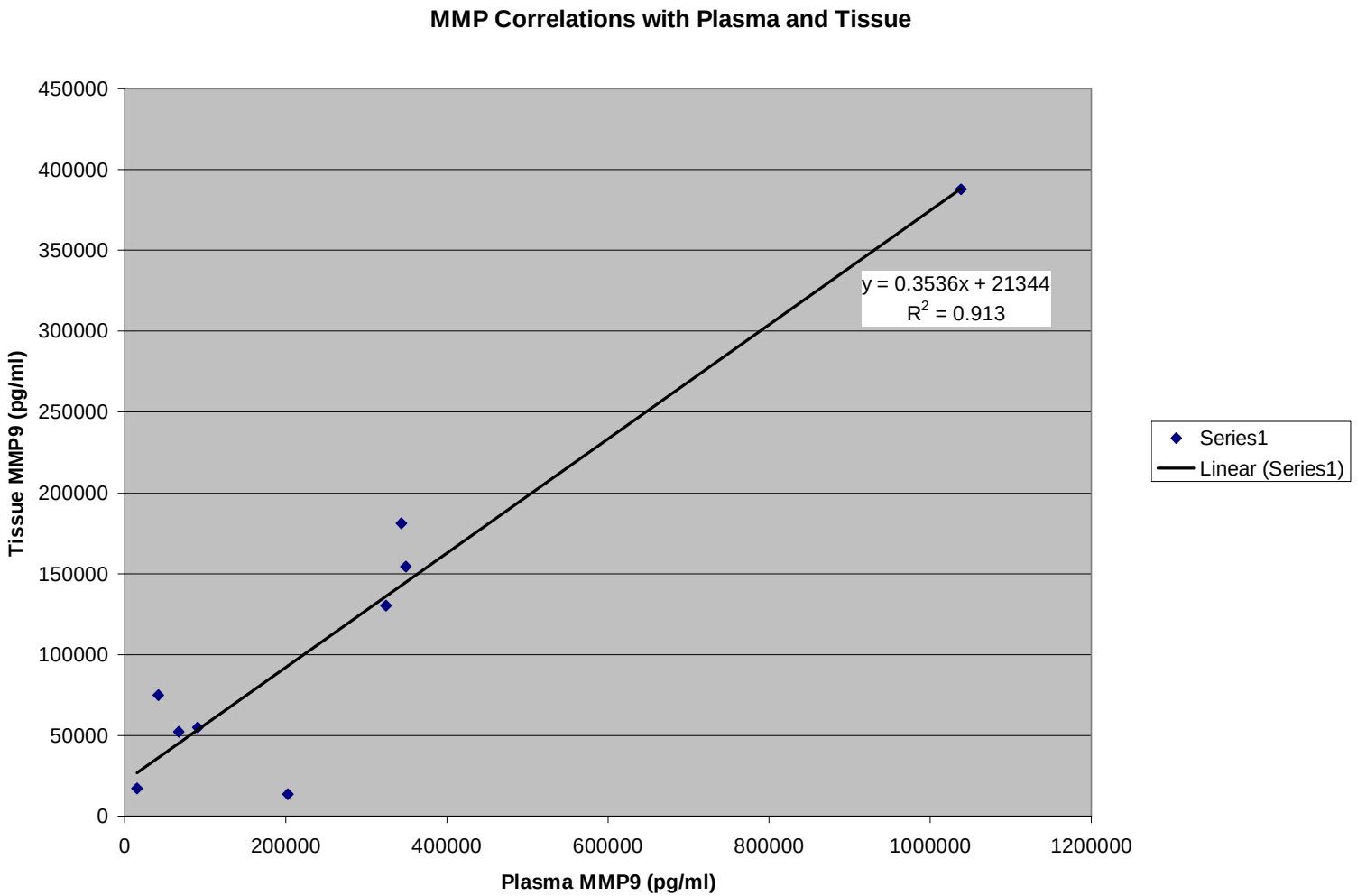
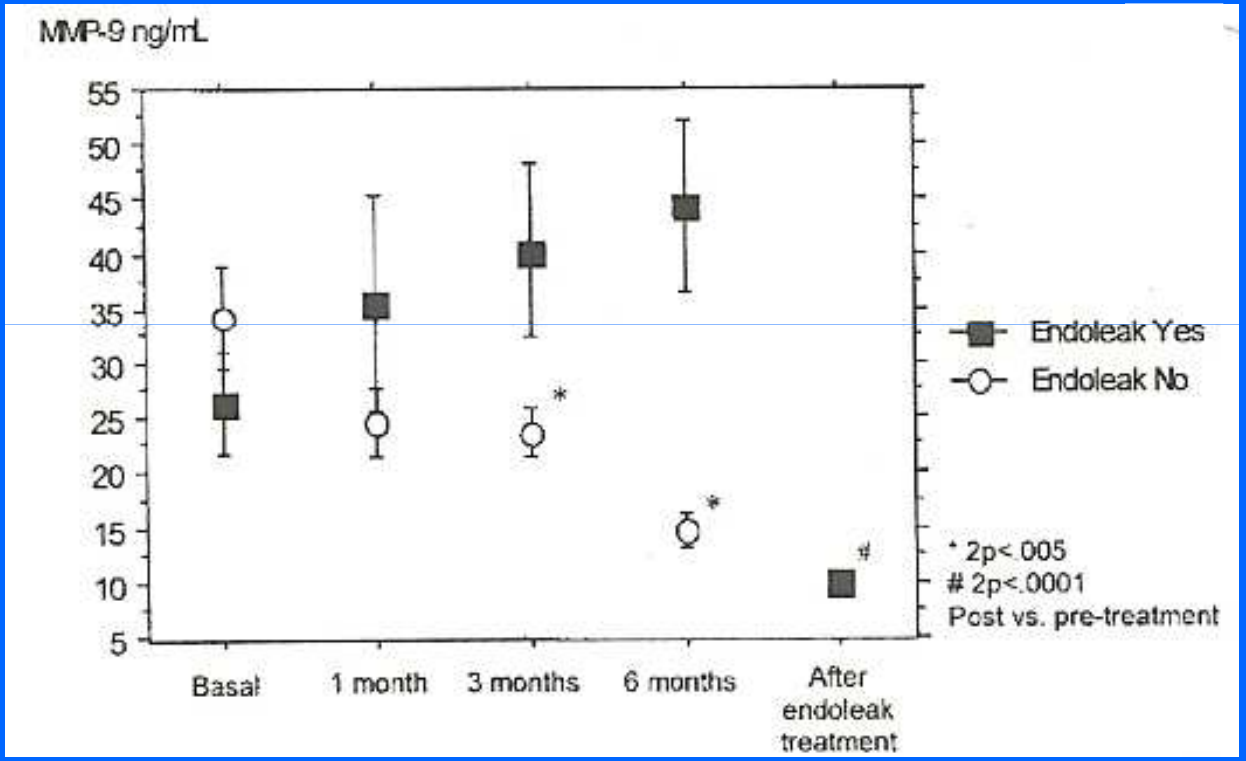

MMP Correlations with Plasma and Tissue
Tissue MMP9 (pg/ml)
Plasma MMP9 (pg/ml)
450000
400000
350000
300000
250000
200000
150000
100000
50000
0
0
200000
400000
600000
800000
1000000
1200000
y = 0.3536x + 21344
R2 = 0.913
Series1
Linear (Series1)

Figure 5.

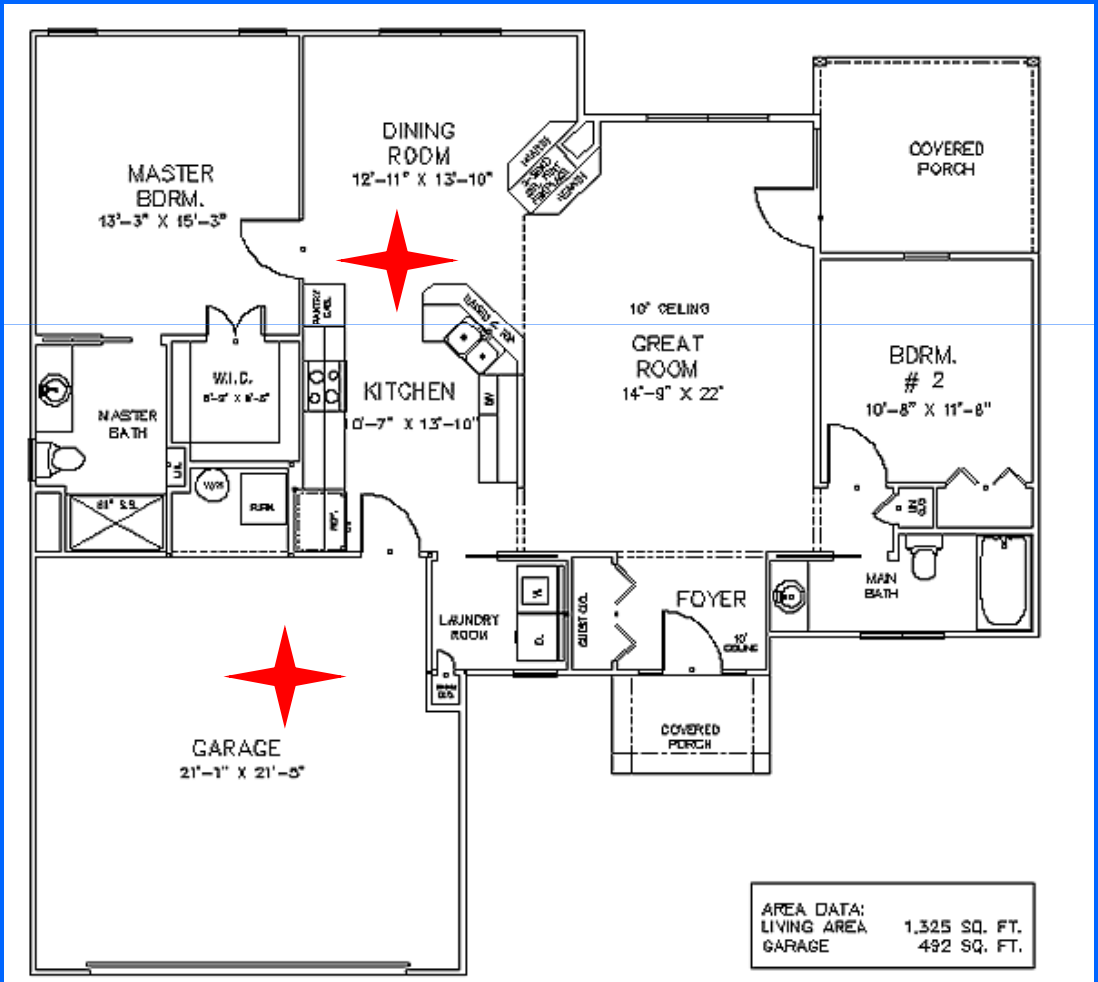
Serum MMP levels successfully predict stent graft failure



Sangiorgi G, et al. *Circulation* 2001;104[suppl I]:I-288-I-295.

“RNA Signature”

- DNA is blueprint
- RNA tells us what rooms (systems) are actively being worked on



Gene–Centric Functional Genome–Wide Discovery

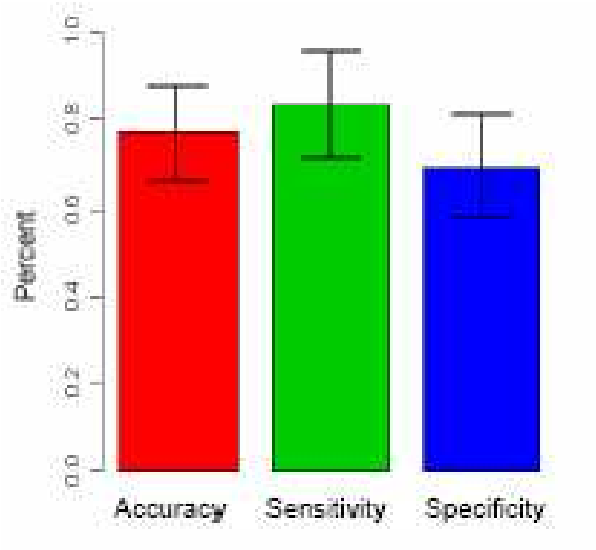
High Throughput Laboratory

- 33,000–SNP genome–wide scans with 500 stratified samples using a phenotype–driven pooling strategy
- Daily real–time data analysis for immediate reflex replication
- Technology excels for both genotyping and pooled–sample studies

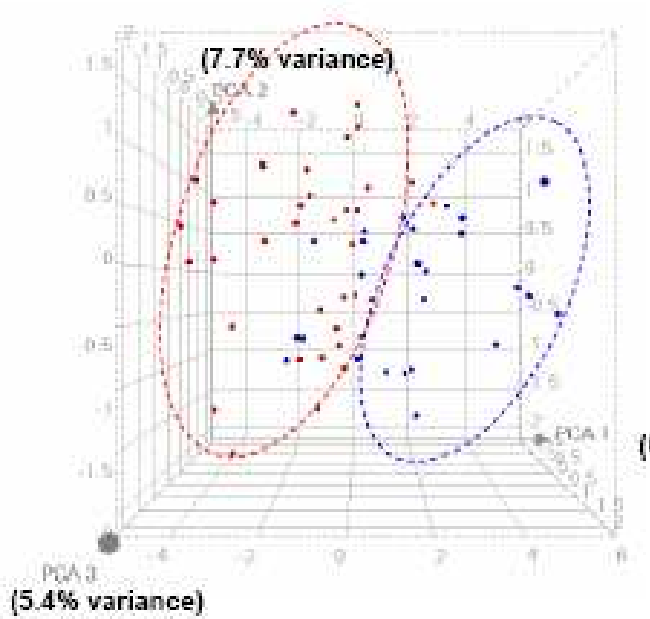
Applied Biosystems Human Whole Genome Survey Microarray

RNA “Signature” in peripheral blood

A.



B.



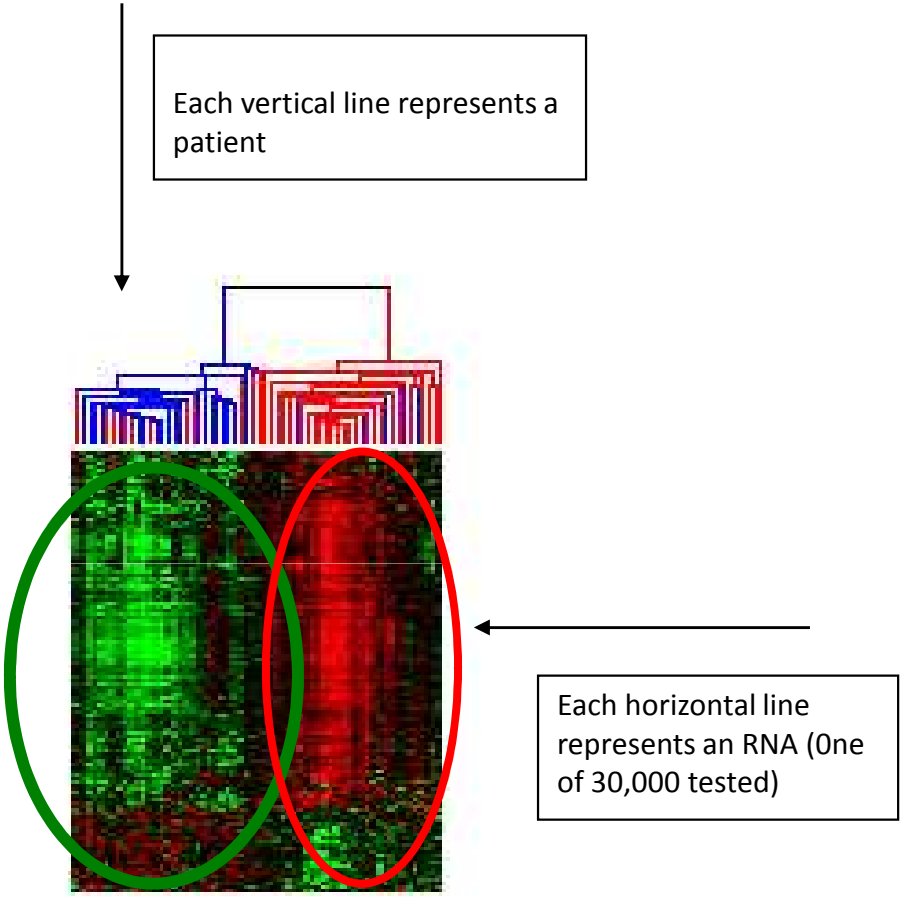
How do these sensitivities/specificities compare with other screeing tests?

PSA Test Guidelines for Prostate Cancer Inadequate
July 7, 2005

A major study in JAMA has found that prostate-specific antigen (PSA) test is a less reliable treatment indicator for prostate cancer than previously believed.

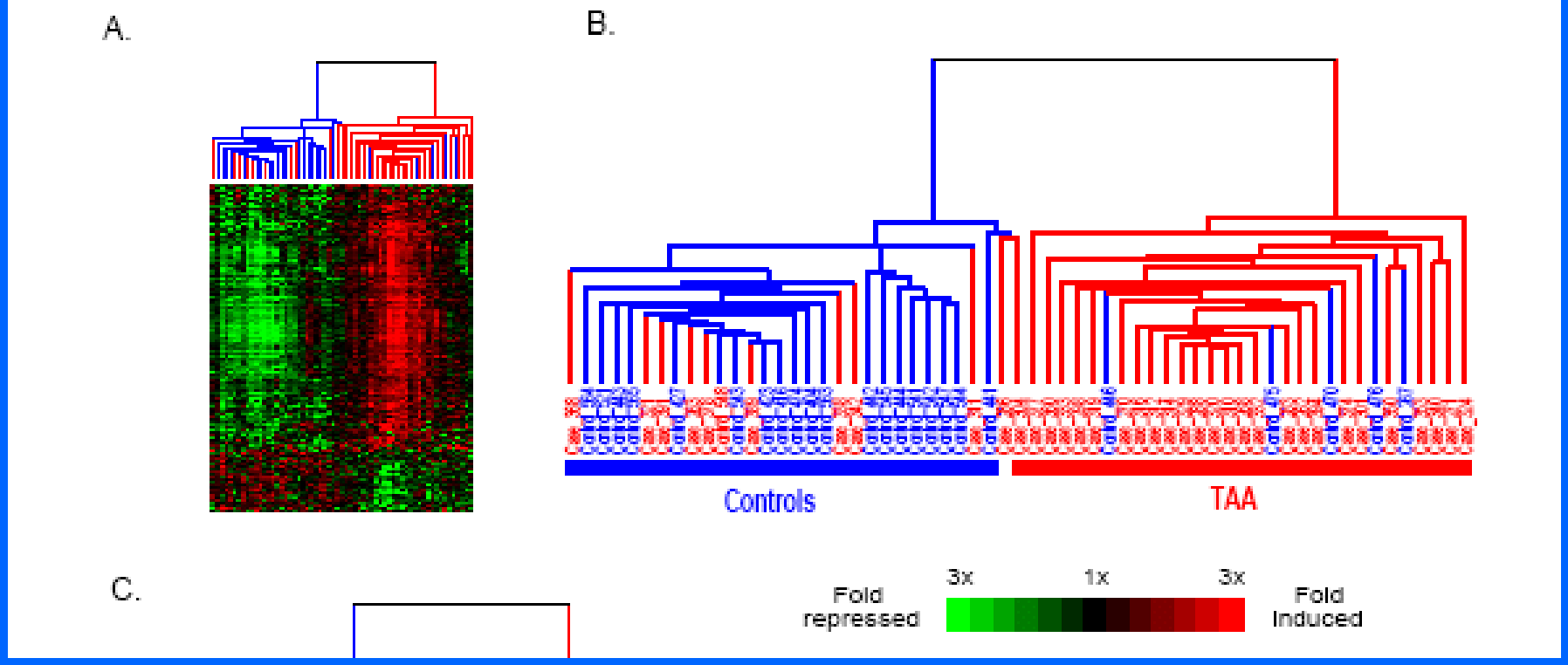
A PSA reading of 4.1 detected only 20.5% of existing cancers, while also mistakenly diagnosing cancer (i.e., giving a false positive) in 6.2% of men studied.

"There is no cutpoint of PSA with simultaneous high sensitivity and high specificity. “



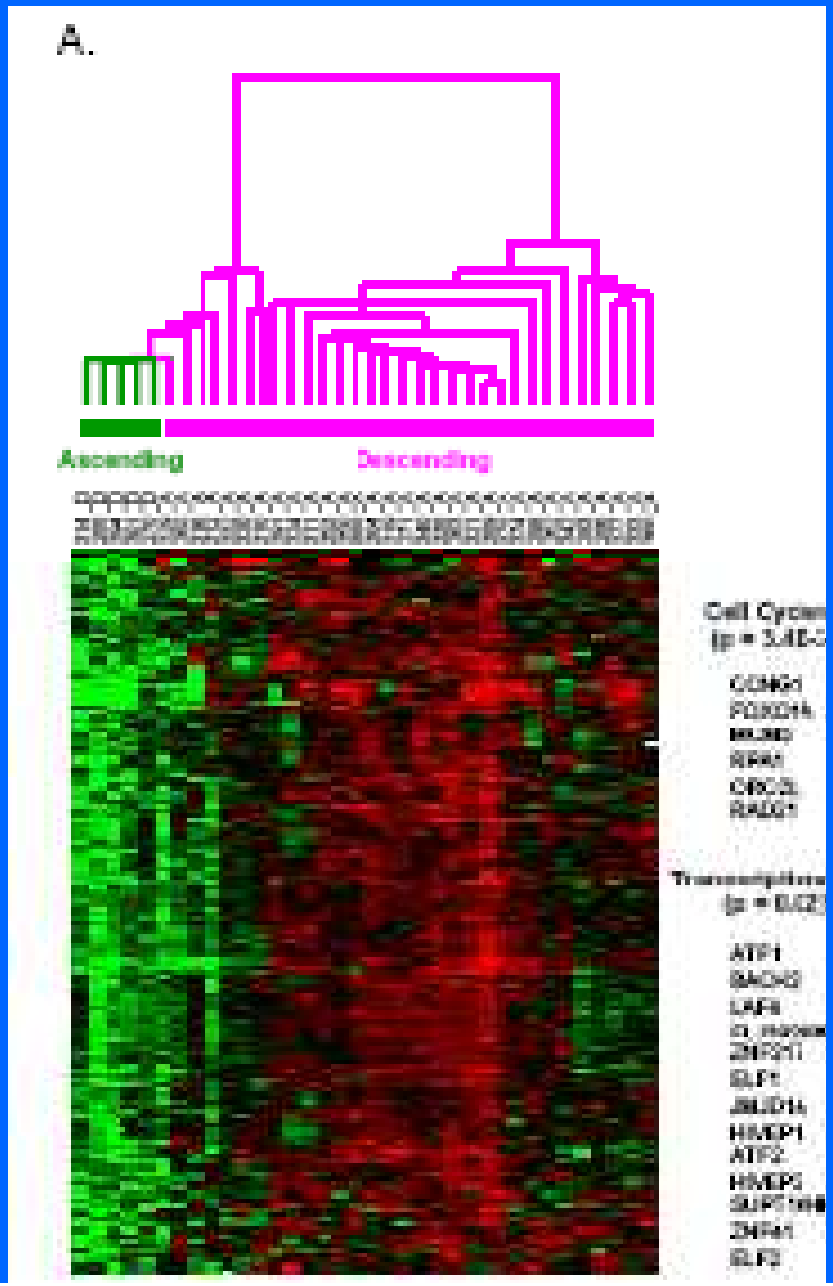
Hierarchical clustering diagrams.

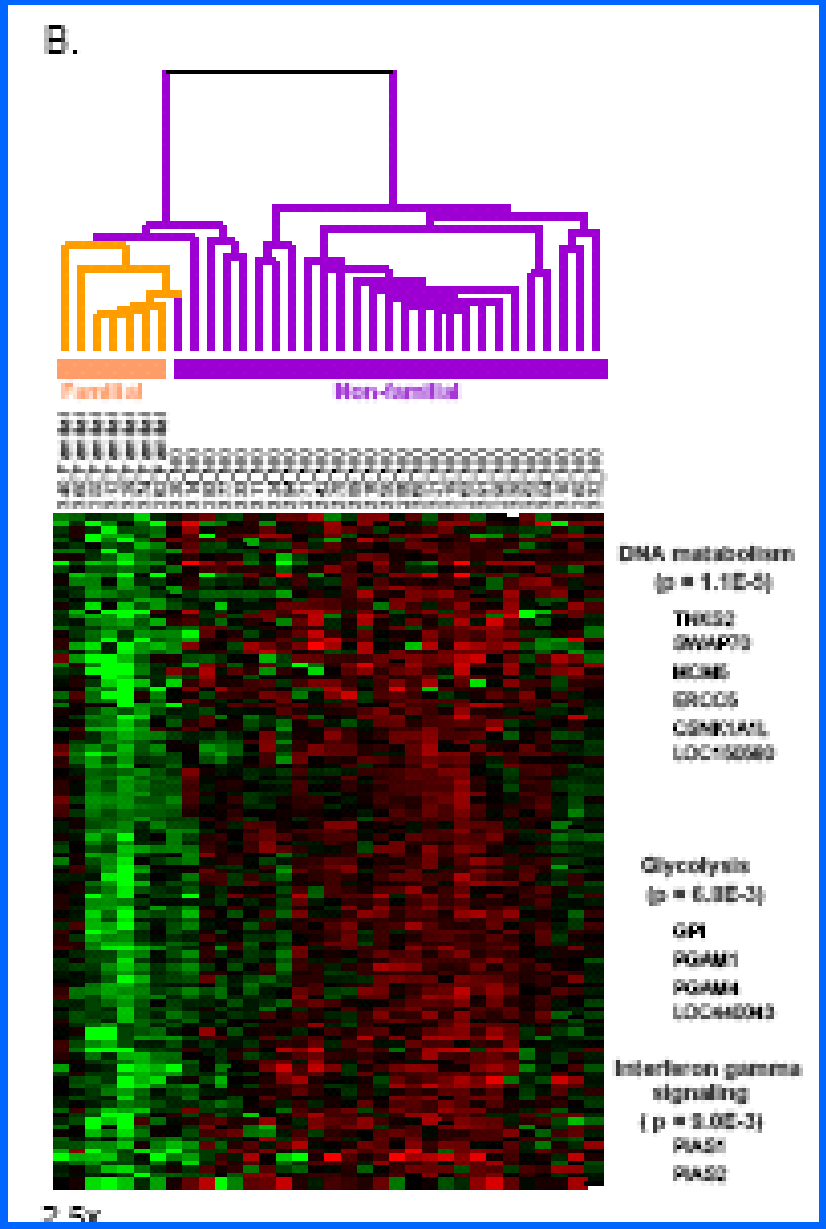
Figure 1

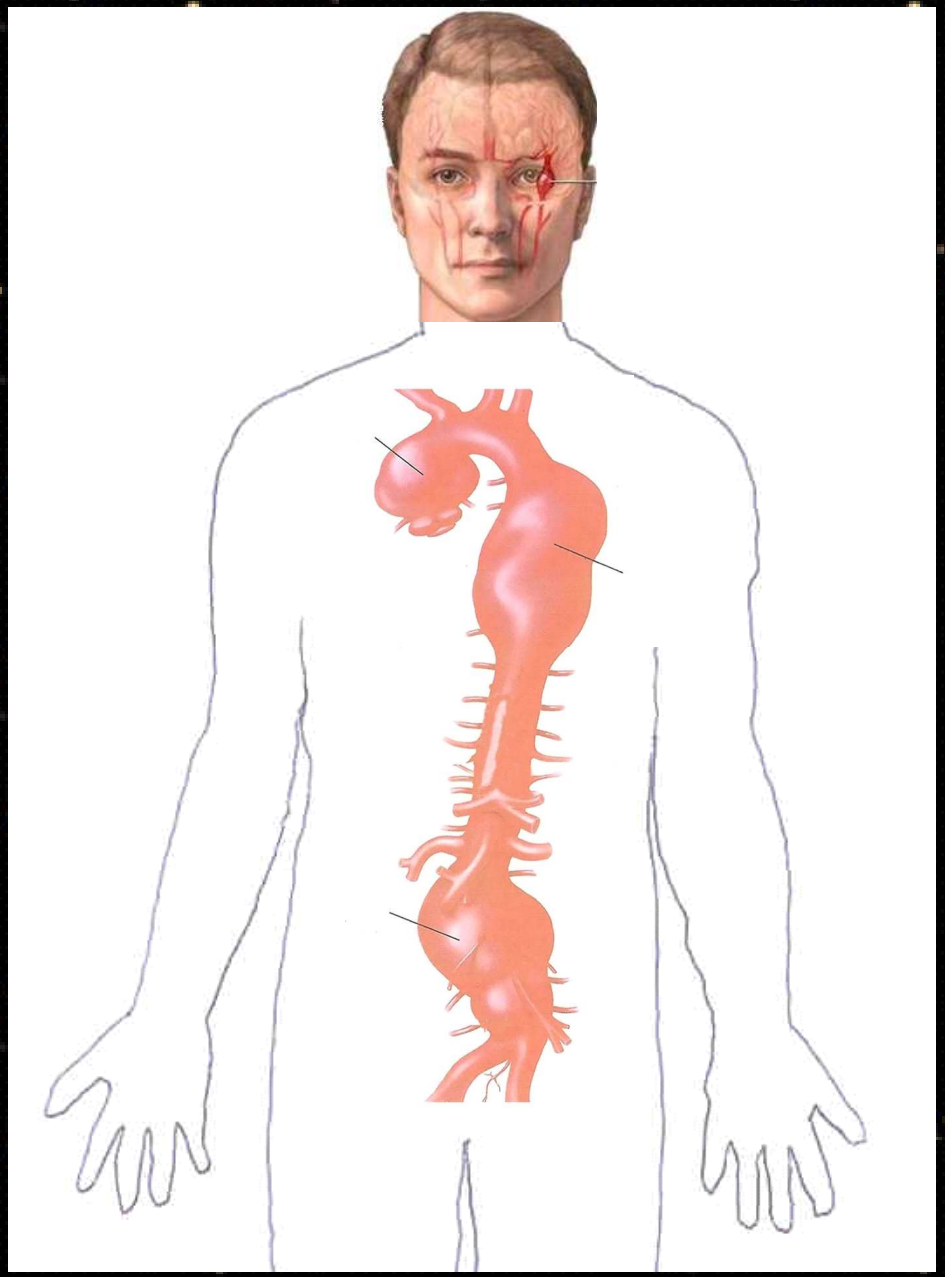


"RNA Signature" genes identified make "physiologic sense": proteolyis, apoptosis, inflammation

Gene Symbol	Gene_Name	Target RefSeqs	Asc/Desc Ratio (array)	Asc/Desc Ratio (TaqMan)
AFF3	AF4/FMR2 family, member 3	NM_002285	2.79	2.27
BACH2	BTB and CNC homology 1, basic leucine zipper transcription factor 2	NM_021813	2.38	2.22
ZNF41	zinc finger protein 41	null	2.33	1.53
ATF2	activating transcription factor 2	NM_001880	2.20	1.58
HIVEP2	human immunodeficiency virus type I enhancer binding protein 2	NM_006734	2.08	1.53
HIVEP1	human immunodeficiency virus type I enhancer binding protein 1	NM_002114	2.00	1.44
ATF1	activating transcription factor 1	NM_005171	1.78	1.33
ORC2L	origin recognition complex, subunit 2-like (yeast)	NM_006190	1.66	1.55
FOXO1A	forkhead box O1A (rhabdomyosarcoma)	NM_002015	1.63	1.48
RAD21	RAD21 homolog (S. pombe)	NM_006265	1.62	1.29
ELF1	E74-like factor 1 (ets domain transcription factor)	NM_172373	1.61	1.35
ELF2	E74-like factor 2 (ets domain transcription factor)	NM_006874	1.59	1.35
MCM3	MCM3 minichromosome maintenance deficient 3 (S. cerevisiae)	NM_002388	1.57	1.45
RPA1	replication protein A1, 70kDa	NM_002945	1.52	1.53
ZNF217	zinc finger protein 217	NM_006526	1.46	2.02
JMJD1A	jumonji domain containing 1A	NM_018433	1.44	1.55
SUPT16H	suppressor of Ty 16 homolog (S. cerevisiae)	NM_007192	1.43	1.63
CCNG1	cyclin G1	NM_004060	1.39	1.53


A.
Ascending
Descending


B.
Familial
Non-familial
DNA metabolism
(p = 1.1E-5)
TK852
SWAP70
MCM5
ERCC5
CSNK1A1L
LOC150580
Glycolysis
(p = 6.3E-3)
GPI
PGAM1
PGAM4
LOC440043
Interferon gamma
signaling
(p = 9.0E-3)
PIAS1
PIAS2



Intervention criteria for the future…

- Size
- Symptoms
- Family history
- Mechanical properties
- Biomarkers
  - MMPs
  - RNA Signature