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PERSPECTIVES

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"Big Data" Analyses Underlie Clinical Discoveries at the Aortic Institute

Mohammad A. Zafar[a], Bulat A. Ziganshin[a], Yupeng Li[b], Nicolai P. Ostberg[a,c], John A. Rizzo[d], Maryann Tranquilli[a], Sandip K. Mukherjee[a], and John A. Elefteriades[a,*]

[a]*Aortic Institute at Yale New Haven Hospital, Yale University School of Medicine, New Haven, CT, USA;* [b]*Department of Political Sciences and Economics, Rowan University, Glassboro, NJ USA;* [c]*New York University Grossman School of Medicine, New York, NY, USA;* [d]*Department of Economics and Department of Preventive Medicine, Stony Brook University, Stony Brook, NY, USA*

This issue of the *Yale Journal of Biology and Medicine* (*YJBM*) focuses on Big Data and precision analytics in medical research. At the Aortic Institute at Yale New Haven Hospital, the vast majority of our investigations have emanated from our large, prospective clinical database of patients with thoracic aortic aneurysm (TAA), supplemented by ultra-large genetic sequencing files. Among the fundamental clinical and scientific discoveries enabled by application of advanced statistical and artificial intelligence techniques on these clinical and genetic databases are the following: **From analysis of Traditional "Big Data" (Large data sets)**. 1. Ascending aortic aneurysms should be resected at 5 cm to prevent dissection and rupture. 2. Indexing aortic size to height improves aortic risk prognostication. 3. Aortic root dilatation is more malignant than mid-ascending aortic dilatation. 4. Ascending aortic aneurysm patients with bicuspid aortic valves do not carry the poorer prognosis previously postulated. 5. The descending and thoracoabdominal aorta are capable of rupture without dissection. 6. Female patients with TAA do more poorly than male patients. 7. Ascending aortic length is even better than aortic diameter at predicting dissection. 8. A "silver lining" of TAA disease is the profound, lifelong protection from atherosclerosis. **From Modern "Big Data" Machine Learning/Artificial Intelligence analysis**: 1. Machine learning models for TAA: outperforming traditional anatomic criteria. 2. Genetic testing for TAA and dissection and discovery of novel causative genes. 3. Phenotypic genetic characterization by Artificial Intelligence. 4. Panel of RNAs "detects" TAA. Such findings, based on (a) long-standing application of advanced conventional statistical analysis to large clinical data sets, and (b) recent application of advanced machine learning/artificial intelligence to large genetic data sets at the Yale Aortic Institute have advanced the diagnosis and medical and surgical treatment of TAA.

*To whom all correspondence should be addressed: John A. Elefteriades, MD, PhD (hon), Aortic Institute at Yale New Haven Hospital, Yale University School of Medicine, New Haven, CT; Email: john.elefteriades@yale.edu; ORCID: 0000-0001-6255-8139.

Abbreviations: TAA, thoracic aortic aneurysm; WES, Whole Exome Sequencing; BSA, Body Surface Area; AHI, aortic height index; IMT, intima media thickness; BART, Bayesian Additive Regression Trees; AUROC, area under the receiver operator curve.

Keywords: thoracic aortic aneurysm, aortic root, ascending aorta, descending aorta, aortic dissection, type A dissection, type B dissection, natural history, risk prediction, big data, machine learning, database

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INCEPTION OF THE AORTIC INSTITUTE AND ITS DATABASE

The genesis of the Aortic Institute at Yale New Haven Hospital transpired on a crisp spring Saturday morning in 1993 when one of the authors of this manuscript, Dr. Elefteriades, happened to be solely in charge of his small children. Lo and behold, a call came in from preeminent cardiologist Dr. Lawrence Cohen, who was atypically distraught. A Yale Professor's wife, a patient of Dr. Cohen's, was dying in the Emergency Room, having just suffered a ruptured Type A aortic dissection. Dr. Elefteriades left his two children with a barely known neighbor and rushed to the hospital. He performed successful emergency surgery, replacing the dissected aorta. That is how Dr. Elefteriades met Dr. John Rizzo, a Professor of Epidemiology at Yale, at the bedside of his deteriorating wife—before the life-saving surgical intervention. It was Dr. Rizzo's wife, Ms. Carmela Kolman, who needed the operation and who was ultimately restored to decades of health.

Before the near-catastrophic aortic dissection event, Ms. Kolman had known of the enlargement of her aorta, which did not meet contemporary criteria for preventative surgical intervention. As Ms. Kolman recovered, Dr. Elefteriades and Dr. Rizzo had conversations during evening rounds about how Carmela's case pinpointed the need for improved, scientifically based intervention criteria. Ms. Kolman had been under surveillance for her modestly dilated ascending thoracic aortic aneurysm (TAA). Contemporary criteria had failed her. Dr. Elefteriades and Dr. Rizzo mused about potentially writing a paper together someday about aortic disease, and those discussions proved to be the genesis of the Aortic Institute at Yale.

It was specifically Dr. Rizzo's ability to develop techniques and formulas for handling the ensuing aortic aneurysm "Big Data" repository, that permitted the scientific advances in aortic disease which followed that inauspicious start in the Yale Emergency Room in 1993.

Since then, the Aortic Institute at Yale New Haven Hospital has evolved into one of the largest multidisciplinary clinical and research centers in the world dedicated to the care of patients with thoracic aortic disease. The Aortic Institute at Yale is among the first, if not the very first, such formally designated centers in the country. The Aortic Institute team has published over 350 papers on aortic disease over the last three decades, all founded on our database, one of the largest such repositories extant, with Ms. Carmela Kolman as patient #1 [1,2]. Most large academic or clinical care hospitals now harbor an "Aortic Institute" or equivalent, our own having been founded and proliferating via analysis of large data sets.

CONVENTIONAL "BIG DATA" ORIGINS OF AORTIC INSTITUTE RESEARCH FINDINGS

At the inception of the Aortic Institute in 1993, "Big Data" carried a different connotation than it does today. The Aortic Institute was from inception considered a "Big Data" endeavor not in today's sense of machine learning analysis of large data sets, but rather by virtue of the large number of patients enrolled in its clinical programs and codified in its "Database." Instead of dozens or hundreds of patients, the Aortic Institute, by virtue of its robust clinical program, rapidly amassed a database including thousands of patients with aortic disease—hailing from around the country and the world. The sheer volume of data contained in the Yale Aortic Institute Database set this apart from earlier efforts and permitted detailed scientific analysis of clinical behavior of the aorta. Through advanced statistical techniques developed by Dr. Rizzo for analyzing aortic disease, many novel, impactful clinical insights were able to be achieved. For example, Dr. Rizzo devised a novel "instrumental variables" approach for calculating aortic growth, which minimized the deleterious impact of measurement error in assessing aortic diameter. He expressed this as [3]:

$\ln S^{M}_{L} - \ln S^{M}_{F} = \beta 0T \text{ X } \beta 1T * \text{RISK}$, where S^{M}_{L} is the last aortic size, $\ln S^{M}_{F}$ is the first aortic size, T is time, and RISK is a compilation of empirically determined risk factors. Note that at T=0, the first and last measured size must be the same.

This advanced analytic approach formed the basis for many future investigations. This represented cutting edge analysis for the time period.

The Database currently harbors information on over 4,000 patients with aortic disease and detailed imaging (including verified re-measurements of aortic dimensions) on close to 3,000 patients. The database also includes Whole Exome Sequencing (WES) of blood or saliva of 512 patients, and WES of 1,260 aortic tissue specimens resected by Dr. Elefteriades during aortic surgery. Each WES includes base identification (A (adenine), G (guanine), C (cytosine), and T (thiamine)) of approximately 20,000 protein-coding genes and 30 million base pairs, which is approximately 1-2% of the entire human genome [4]. Our sample set totals approximately 1,800 human genetic sequences in patients bearing thoracic aortic aneurysms. The blood and saliva sequencing has been performed by the Yale Clinical Genetics Laboratory, under the direction of Dr. Allen Bale. The sequencing and analysis of the aortic tissue specimens has been performed via collaboration with Regeneron Genetics Center and Dr. Wendy Chung of Columbia University. This work forms the basis for the PhD candidacy of the Aortic Institute's own Dr. Bulat Ziganshin, one of our long-term Research Directors.

The patient and image volume can be considered "Big Data" in the conventional sense. The huge amount of genetic data can be considered "Big Data" in the modern sense. We will present below key findings from the "Conventional" and "Modern" Big Data efforts.

In addition to our work with Dr. Rizzo, Nicolai Ostberg from our team, and Dr. Wei Sun and Dr. Liang Liang from Georgia Tech University and University of Miami, have analyzed our data using advanced Artificial Intelligence techniques, resulting in several new insights [5-8].

Our previous contribution to the 2008 issue of the *Yale Journal of Biology and Medicine* (*YJBM*) outlined several initial critical insights into the "Playbook" of thoracic aortic disease, gleaned from clinical and laboratory investigations undertaken at that time [9]. Our TAA and dissection database has been the foundation of these investigations, allowing us to unravel the natural history of aneurysms of the thoracic aorta, so as to better guide optimal timing for surgical treatment. Aside from development of size criteria for surgical intervention, the large database has permitted nearly innumerable other insights to be achieved. Some of this work is summarized here – in a 15-year follow-up to our initial *YJBM* publication.

Initial natural history efforts. Our earliest natural history studies, comprising a few hundred ascending and descending TAA patients, revealed sharp "hinge points" in the aortic size at which the risk of dissection and rupture escalated dramatically: By the time the ascending thoracic aorta reached a size of 6.0 cm and the descending thoracic aorta a size of 7.0 cm, patients incurred a 32% and 43% risk, respectively, of dissection or rupture [10-12]. Accordingly, we recommended prophylactic surgical intervention *before* those hinge points: at 5.5 cm for aneurysms of the ascending aorta, and 6.5 cm for the descending aorta. These data and analysis formed the basis of the 2010 US and 2014 European thoracic aortic disease management "Guidelines" [13,14].

Of course, conclusions drawn can only be as accurate as the underlying data, for which we have expended forethought and effort.

Measurement standardization. What began as a one-page clinical patient visit datasheet, thanks to the vision and drive of the inimitable Ms. Maryann Tranquilli, the nursing backbone of the Aortic Institute since its inception, has morphed into the large, computerized database described above. On occasion, despite the advanced computerization, we return to the original datasheets for special tidbits of information that Ms. Tranquilli entered for which there is no computer column, or for our hand-drawn surgical diagrams. The original datasheets fill dozens of "old school" three-ring binders.

Because of the vagaries of aortic measurement, [15] we have remeasured and reanalyzed all radiographic images in every one of the database patients – totaling over 10,000 thoracic aortic measurements—keeping in mind all the various important nuances associated with aortic measurement outlined by our team [15,16].

Continued database follow-up for clinical outcomes. We continue to complete careful clinical and survival follow-up and precise cause of death determination for each patient, following our comprehensive six-pronged approach, entailing clinical office visits and notes; phone calls with patients and families; referring physician follow-up; electronic medical record and chart review; online database mortality inquiry; online obituary search; and retrieval and analysis of State-issued death certificates [17]. This has enabled us to evaluate both thoracic aorta-specific mortality and all-cause mortality endpoints. To make clinical sense of this granular data and extend findings to directly improve aortic disease patient care paradigms, we have developed and employed advanced statistical methods and risk prediction models under Dr. Rizzo's guidance, such as the instrumental variables exponential model for aneurysm growth rate estimation and lifetime aneurysm complication risk estimations [3].

SPECIFIC FINDINGS AND INSIGHTS ENABLED BY OUR *CONVENTIONAL* "BIG DATA" EFFORTS

The remainder of this paper will build on our *YJBM* 2008 article [9] and focus on specific novel insights into the Playbook of TAA—spanning natural history, latest intervention criteria, genetics, and early diagnosis of asymptomatic aneurysm-bearing individuals in the general population.

Left-shift in threshold for surgical intervention. By accruing detailed clinical, survival, and radiologic information on each of the patients in the database – specifically regarding (1) the increase in the size of the aneurysmal aorta over time, and (2) the precise aortic dimensions at which occur the lethal complications - dissection (internal splitting of the aortic layers) and rupture – our team has been able to refine the aforementioned surgical thresholds, articulating even more robust evidence-based intervention criteria for preemptive surgical repair of the ascending aorta. Specifically, our most recent data indicated a hinge point about a half centimeter "earlier" than our original 5.5 cm. Accordingly, we recommended a "left-shift" to intervention as soon as 5 cm [18,19]. This recommendation has indeed been implemented in the most recent US 2022 Guidelines for thoracic aortic disease management [20]. Implementation in the 2023 European Guidelines is pending.

Body size and height corrections for aortic prediction. In 2006, our group proposed indexing aortic size to body surface area, in order to refine size criteria for

surgical intervention for very small or very large individuals [21]. Of course, logic dictates that one cannot use the same size criteria for all patients, because body size varies. Indeed, for example, one cannot apply the same aortic intervention criteria for Shaquille O'Neal as for Simone Biles. Although we generally consider 4.0 cm the upper limit of normal size for the ascending aorta, an aortic size of 4.5 cm in a very large individual likely lies at the patient-specific upper limit of normal. The same dimension, however, may lie in the danger zone for a tiny individual. We initially used Body Surface Area (BSA) as our morphometric basis, producing tables of acceptable aortic size based on BSA. BSA is based on both height and weight. Later, however, we wondered how the aorta would "know" if a patient had gained weight—or why it would care.

With those considerations in mind, we concentrated on height alone for estimation of clinical risk at various aortic dimensions. Height, largely genetically predetermined, we thought, might correlate better with aortic size. To address this, we introduced and validated the "aortic height index," or AHI [$AHI=\frac{Aortic\ Diameter\ (cm)}{Height\ (m)}$]. We found AHI an accurate predictor of adverse events in ascending aneurysm patients—more accurate, in fact, than indices such as BSA which factor in patient weight [22]. Armed simply with patient aortic size and height, clinicians can accurately derive the risks of aortic rupture, dissection, and death utilizing our ensuing nomogram (Figure 1). The effectiveness of this criterion has been highlighted by Demertzis and Grego, from Switzerland, who found that retrospective application of this predictive tool would have theoretically protected a full 91% of their patients from aortic dissection [23]. Furthermore, the 2022 US Aortic Disease Management Guidelines now recommends indexing aortic size to patient height [20].

Aortic root dilatation more dangerous than mid-ascending aortic dilatation. Prior studies and current guidelines consider the entire ascending thoracic aorta—from the aortic annulus to the take-off of the left subclavian artery—as one "unit." Thus, recommendations for operative repair have not taken into account whether a patient has aortic root dilation (ie, aneurysm of the very proximal clover-leaf portion of the aorta, composed of the three sinuses of Valsalva) or, rather, an aneurysm confined to the more cylindrical, supracoronary mid-ascending aorta.

Our team was often asked which of these two patterns of dilation is more dangerous—a very valid question given the anatomic, physiologic, and embryologic differences between the two segments: the aortic root is derived from the secondary heart field, a lateral plate mesoderm derivative, while the ascending aorta and arch are neural crest derived [24].

We found that these two segments do indeed have unique natural histories, and that a given level of dilatation is more "malignant" in the root than in the ascending portion [25].

Does bicuspid aortopathy require earlier surgical intervention? A bicuspid aortic valve is the most common congenital disorder afflicting the human heart, first chronicled by Leonardo da Vinci over half a millennium ago [26,27]. Bicuspid aortic valve patients are strongly predisposed to developing ascending aneurysms, and aortic dissections [28-30].

For quite some time it was believed that bicuspid aortic valve associated aneurysms were a virulent entity, similar to Marfan aortas, with 2010 US guidelines recommending surgical intervention at aortic diameters as low as 4.0/4.5 cm [13].

We recently examined and compared the long-term natural behavior of nearly 600 bicuspid ascending aortic aneurysms, and 2,000 trileaflet aortic valve associated ascending aortic aneurysms [31]. We found "hinge points" for both bicuspid aortic valve and trileaflet aortic valve patients at the 5.0 cm mark, but hazard rates for bicuspid patients were actually *lower*, contrary to prior thought (Figure 2). Ten-year adverse event-free survival was significantly better for bicuspid patients. Thus, bicuspid aortic valve emerged not only not harmful but actually "protective" against adverse aortic events, compared to trileaflet valve patients.

These findings argue against earlier intervention in bicuspid aortic valve patients. Our recommendation, in line with that of the latest societal guidelines, is to consider surgical intervention at 5.0 cm in both bicuspid and trileaflet valve patients, at high-volume expert aortic centers [20,32].

Natural history of descending thoracic aortic aneurysm. Thus far, our discussion has focused on the ascending aorta. It is important to understand that TAA is actually two different diseases separated at the ligamentum arteriosum, in line with different embryological origins [33]. The descending aorta beyond the ligamentum is derived from the mesoderm whereas the ascending aorta is derived from the neural crest (Figure 3a) [34]. Above (proximal) to the ligamentum, the aorta is thin, but not atherosclerotic. Ascending aneurysms are generally not calcified and do not contain thrombus. Below the ligamentum, as with abdominal aortic aneurysms, heavy arteriosclerosis, irregular contours, a high thrombus burden, and calcification predominate.

Therefore, we undertook separate studies to investigate the natural history of descending thoracic and thoracoabdominal aortic aneurysms. We analyzed aortic diameters, growth rates, and long-term complications (ie, descending aortic rupture, acute descending (Type B) aortic dissection, and death) of almost 1,000 descending/thoracoabdominal patients from our database, yielding

	Aortic Size (cm)									
	3.5	**4.0**	**4.5**	**5.0**	**5.5**	**6.0**	**6.5**	**7.0**	**7.5**	**8.0**
Height (m)										
1.40	2.50	2.86	3.21	3.57	3.93	4.29	4.64	5.00	5.36	5.71
1.45	2.41	2.76	3.10	3.45	3.79	4.14	4.48	4.83	5.17	5.52
1.50	2.33	2.67	3.00	3.33	3.67	4.00	4.33	4.67	5.00	5.33
1.55	2.26	2.58	2.90	3.23	3.55	3.87	4.19	4.52	4.84	5.16
1.60	2.19	2.50	2.81	3.13	3.44	3.75	4.06	4.38	4.69	5.00
1.65	2.12	2.42	2.73	3.03	3.33	3.64	3.94	4.24	4.55	4.85
1.70	2.06	2.35	2.65	2.94	3.24	3.53	3.82	4.12	4.41	4.71
1.75	2.00	2.29	2.57	2.86	3.14	3.43	3.71	4.00	4.29	4.57
1.80	1.94	2.22	2.50	2.78	3.06	3.33	3.61	3.89	4.17	4.44
1.85	1.89	2.16	2.43	2.70	2.97	3.24	3.51	3.78	4.05	4.32
1.90	1.84	2.11	2.37	2.63	2.89	3.16	3.42	3.68	3.95	4.21
1.95	1.79	2.05	2.31	2.56	2.82	3.08	3.33	3.59	3.85	4.10
2.00	1.75	2.00	2.25	2.50	2.75	3.00	3.25	3.50	3.75	4.00
2.05	1.71	1.95	2.20	2.44	2.68	2.93	3.17	3.41	3.66	3.90

= low risk (~ 4% per year) = moderate risk (~ 7% per year) = High risk (~ 12% per year) = severe risk (~ 18% per year)

Light green area indicates low risk, yellow area indicates moderate risk, orange area indicates high risk and red area indicates severe risk.

Figure 1. **Risk of complications (aortic dissection, rupture, and death) in patients with ascending aortic aneurysm as a function of aortic diameter (horizontal axis) and height (vertical axis), with the aortic height index given within the figure**. Light green indicates low risk; yellow, moderate risk; orange, high risk; red, severe risk. Reproduced with permission from: Zafar MA, Li Y, Rizzo JA, Charilaou P, Saeyeldin A, Velasquez CA, et al. Height alone, rather than body surface area, suffices for risk estimation in ascending aortic aneurysm. J Thorac Cardiovasc Surg. 2018;155(5):1938-50. Epub 2018/02/06. doi: 10.1016/j.jtevs.2017.10.140. PMID: 29395211

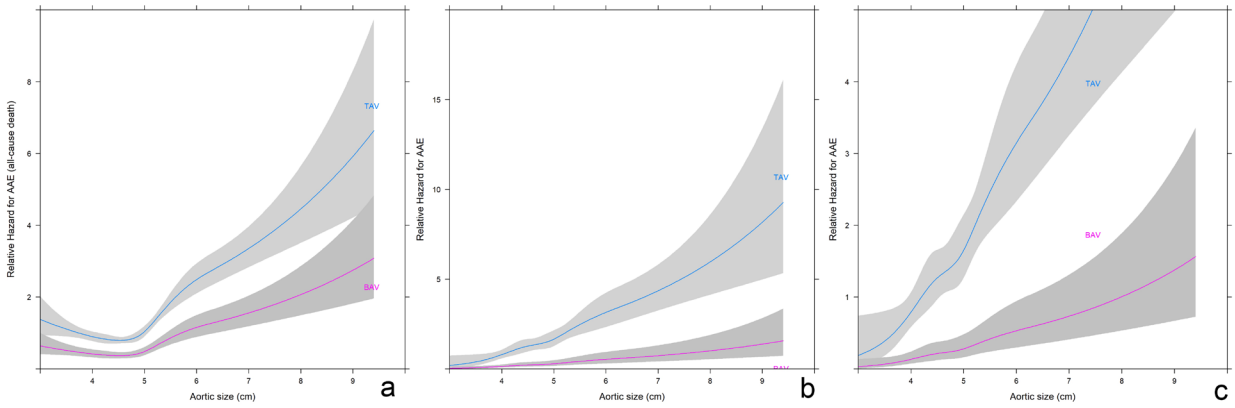
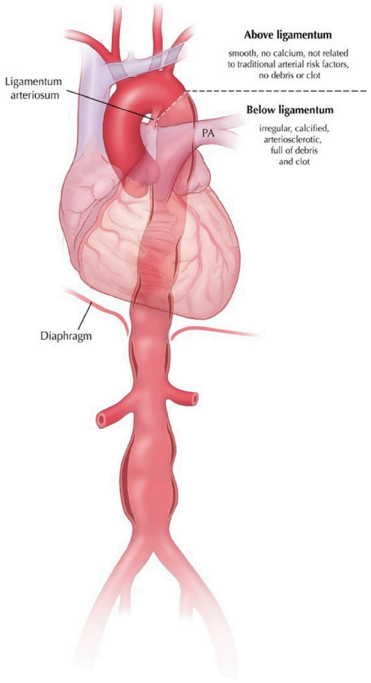
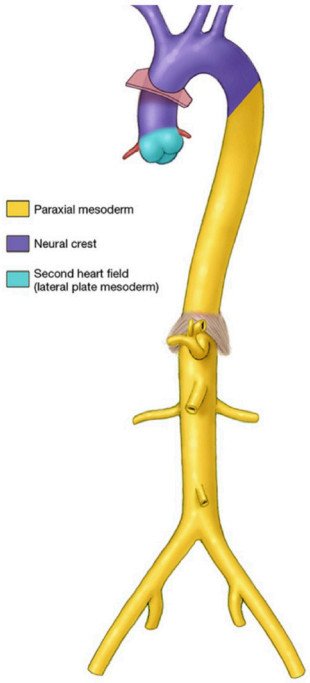


Figure 2. **Regression curves with restricted cubic spline analysis depicting the relationship between aortic size as a continuous variable and adverse aortic events, stratified by aortic valve morphology**. (**a**) all-cause death adverse aortic events (rupture, dissection, and *all-cause death*) (blue line = trileaflet aortic valve, purple line = bicuspid aortic valve), (**b**) ascending aorta specific adverse aortic events (rupture, dissection, and *ascending aortic death*), and (**c**) "zoomed-in" view of 2b. The 95% confidence interval is depicted via shading. Reproduced with permission from: Zafar MA, Wu J, Vinholo TF, Li Y, Papanikolaou D, Ellauzi H, et al. Bicuspid Aortopathy does NOT Require Earlier Surgical Intervention. J Thorac Cardiovasc Surg. 2023. Epub 20230421. doi: 10.1016/j.jtevs.2023.04.017. PMID: 37088130.





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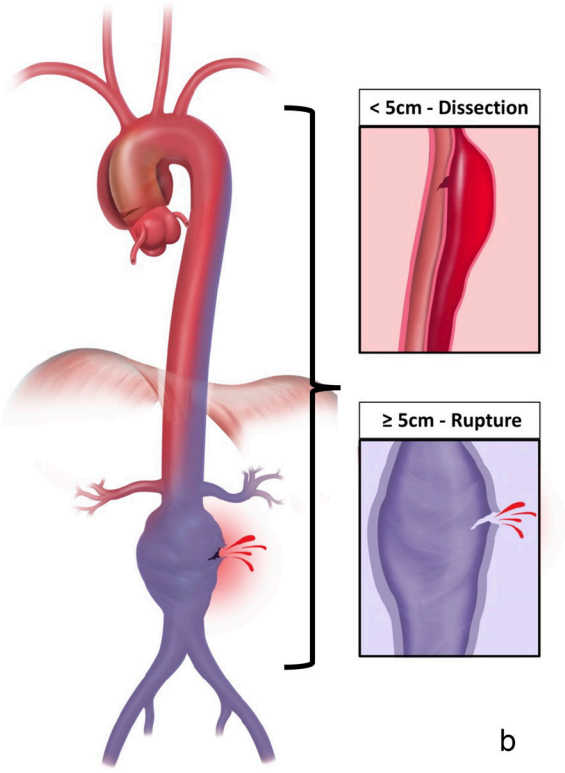

b

Figure 3a. (**Left**) **Note that thoracic aneurysm disease divides naturally into two patterns, separated at the ligamentum**. Above the ligamentum, the aorta is thin, but not atherosclerotic; below the ligamentum, as with abdominal aortic aneurysms, heavy arteriosclerosis and calcification predominate. Figure illustration by Rob Flewell. PA = pulmonary artery. (**Right**) The correspondence of the two atherosclerotic patterns of the aorta with the embryologic origins: ascending from the neural crest and descending/abdominal from the mesoderm. Reproduced with permission from: Elefteriades JA, Farkas EA. Thoracic aortic aneurysm clinically pertinent controversies and uncertainties. J Am Coll Cardiol. 2010;55(9):841-57. doi: 10.1016/j.jacc.2009.08.084. PubMed PMID: 20185035 and Maleszewski JJ. Inflammatory ascending aortic disease: perspectives from pathology. J Thorac Cardiovasc Surg. 2015;149(2 Suppl):S176-83. Epub 20140801. doi: 10.1016/j.jtcvs.2014.07.046. PubMed PMID: 25199476. **3b.** By putting the findings of this study in context with other segments of the aorta, we note the following: The ascending aorta dissects above 5 cm but rarely ruptures without dissection. The abdominal aorta ruptures above 5 cm but rarely dissects. The descending thoracic and thoracoabdominal aorta is a mélange and dissects at small diameters below 5 cm but does not rupture until 5 cm or more. Reproduced with permission from: Zafar MA, Chen JF, Wu J, Li Y, Papanikolaou D, Abdelbaky M, et al. Natural history of descending thoracic and thoracoabdominal aortic aneurysms. J Thorac Cardiovasc Surg. 2021;161(2):498-511 e1. Epub 2020/01/27. doi: 10.1016/j.jtcvs.2019.10.125. PubMed PMID: 31982126.

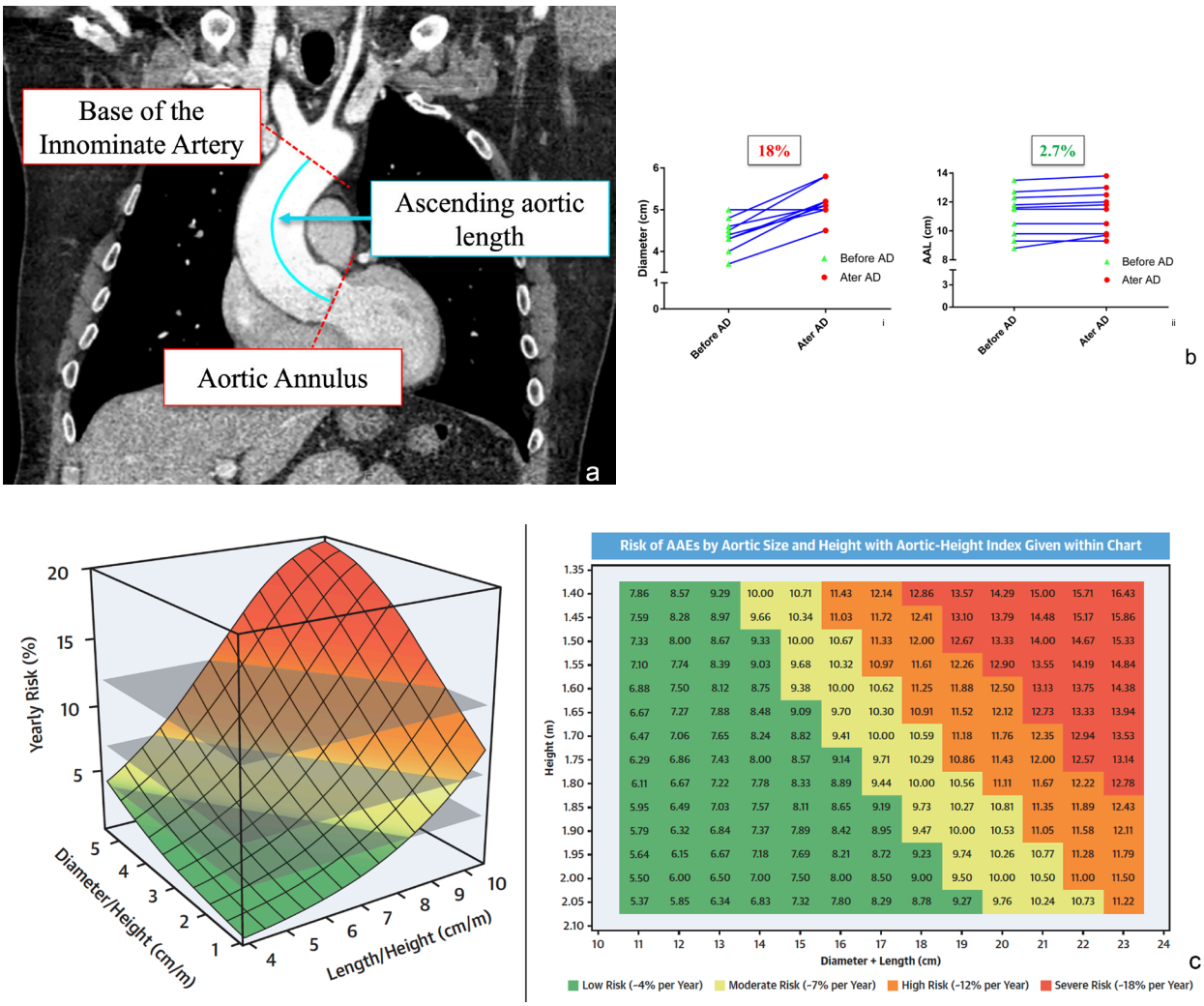

Figure 4a. **Ascending aortic length is measured as distance (blue) from the aortic annulus (red) to the origin of innominate artery (red)**. Reproduced with permission from: Wu J, Zafar MA, Li Y, Saeyeldin A, Huang Y, Zhao R, et al. Ascending Aortic Length and Risk of Aortic Adverse Events: The Neglected Dimension. J Am Coll Cardiol. 2019;74(15):1883-94. Epub 2019/09/19. doi: 10.1016/j.jacc.2019.07.078. PubMed PMID: 31526537. **4b.** Aortic size changes resulting from aortic dissection. (**i**) Aortic diameter increases sharply after aortic dissection. (**ii**) Ascending aortic length along the central line is relatively stable to aortic dissection. AD, aortic dissection; AAL, ascending aortic length. Reproduced with permission from: Wu J, Zafar MA, Li Y, Saeyeldin A, Huang Y, Zhao R, et al. Ascending Aortic Length and Risk of Aortic Adverse Events: The Neglected Dimension. J Am Coll Cardiol. 2019;74(15):1883-94. Epub 2019/09/19. doi: 10.1016/j.jacc.2019.07.078. PubMed PMID: 31526537. **4c.** (**Left**) Prediction plot as a function of diameter height index (x-axis) and length height index (y-axis), with the yearly risk of adverse aortic events presented on the z-axis. (**Right**) Aortic height index (AHI) nomogram as a function of aortic size (diameter + length) (x-axis) and height (y-axis), with the AHI given within cells. The table has a four-tier, color-coded warning system, with red representing the most severe, followed by orange, yellow, and green. AAEs = aortic adverse events. Reproduced with permission from: Wu J, Zafar MA, Li Y, Saeyeldin A, Huang Y, Zhao R, et al. Ascending Aortic Length and Risk of Aortic Adverse Events: The Neglected Dimension. J Am Coll Cardiol. 2019;74(15):1883-94. Epub 2019/09/19. doi: 10.1016/j.jacc.2019.07.078. PubMed PMID: 31526537.

several important and novel insights [35]. We found that the median descending aortic size at acute Type B dissection was 4.1 cm, and 6.6 cm at rupture. It was quite surprising to see that acute Type B dissections were occurring at such small sizes. In fact, 80% of acute Type B dissections occurred at descending aortic diameters below 5.0 cm, most commonly between 3.5-4.0 cm. On the other hand, we found that 93% of acute descending ruptures occurred above a size of 5.0 cm.

What this means is that for the descending thoracic and thoracoabdominal aorta, we cannot predict descending dissection based on size. Thus, we cannot currently define surgical intervention criteria based on size that can protect from Type B dissection [36]. Luckily, Type B dissections are not typically lethal. What we can predict by size is *rupture*. Rupture is very rare before 5.0 cm and becomes common after 6.0 cm. Thus, preemptive surgery at 5.0-5.5 cm can protect from the fatal complications of descending aortic rupture and consequent death.

Putting the present data in context with our aforementioned studies of the ascending aorta, and known data pertaining to the abdominal aorta, we are able to complete the aortic natural history puzzle by pinpointing very different behaviors among three segments of the entire aorta (Figure 3b):

- The ascending aorta dissects above 5.0 cm but rarely ruptures without dissection.
- Rupture following Type A dissection can occur, but pure spontaneous rupture of the ascending aorta, without antecedent dissection, is exceedingly uncommon.
- The abdominal aorta ruptures above 5.0 cm but rarely dissects: in a meta-analysis we performed, we found that the prevalence of isolated abdominal aortic dissection was a mere 1.7% among cases of aortic dissection overall [37].
- So, generally, the ascending aorta does not rupture, and the abdominal aorta does not dissect.
- The descending thoracic and thoracoabdominal aorta on the other hand is a "mélange" of the two segments and dissects at small diameters (often below 5.0 cm) but does not generally rupture until 6.0 cm or more.

Sex differences. We have also studied sex differences in the behavior of descending thoracic and thoracoabdominal aortic aneurysms. Female patients presented with more advanced disease and at an older age [38]. Female patients also exhibited more aggressive disease; indeed, they were more than twice as likely to suffer a complication (dissection, rupture, or aortic death) and exhibited significantly faster descending aneurysm growth rates. Accommodation of body size differences between male and female patients by height indexing is recommended to address this differential outlook.

Ascending aortic length—the neglected dimension. In our natural history studies, we have now progressed to include another morphological parameter, ascending aortic length, and its correlate, aortic tortuosity. Specifically, we have recently identified that *ascending aortic length* is a potent predictor of adverse aortic events, ie, rupture, dissection, and death [39]. As a three-dimensional organ, the aorta manifests both diameter and length. As the aorta elongates, it of necessity becomes more tortuous or C-shaped so as to remain within the confines of the chest cavity.

We defined and measured ascending aortic length as the distance along the centerline from the aortic annulus to the base of the innominate artery (Figure 4a). Our analysis identified two aortic length "hinge points"—at 11.5 cm and 12.5 cm—at which the risk of adverse events increased sharply. Thus, an ascending aortic length threshold of 11.0 cm may serve as an additional intervention criterion for elective ascending aortic aneurysm repair—above and beyond the afore discussed aortic diameter.

We also discovered that, unlike diameter, aortic length is relatively immune to dissection-induced changes. We found that, while diameter increased by 18% due to acute dissection (about 8 mm), the length only increased by less than 3%, further underlining the value of aortic length for risk prediction (Figure 4b).

Based on data from this study, we are able to provide a three-dimensional yearly risk estimation plot that factors in both diameter and length, and a length-based updated nomogram to aid with clinical decision-making (Figure 4c).

Is there a silver lining to thoracic aortic aneurysm disease? Seen above, thoracic aortic aneurysm threatens life severely, especially if not recognized. However, there is a silver lining. Over the course of decades, operating on thousands of ascending aneurysm patients, we noticed in the operating room (when exposing the femoral artery for cannulation) that the arteries of these patients were almost always soft, flexible, and devoid of atherosclerotic calcifications. The femoral arteries were almost always pristine, as seen in adolescents. We noticed that the ascending aorta also appeared non-atherosclerotic, noncalcified, and smooth in contour (Figure 3). We surmised that these patients, it appeared, were somehow protected from atherosclerosis. We therefore initiated a series of clinical investigations to assess this observation.

We analyzed total body calcium score, a late manifestation of atherosclerosis, in our ascending aneurysm patients, compared to controls. We found that in Type A dissection patients and patients with aortic root aneurysms, the calcium score was significantly lower than in control patients, independent of all other atherosclerosis risk factors [40].

We then studied the carotid intima media thickness

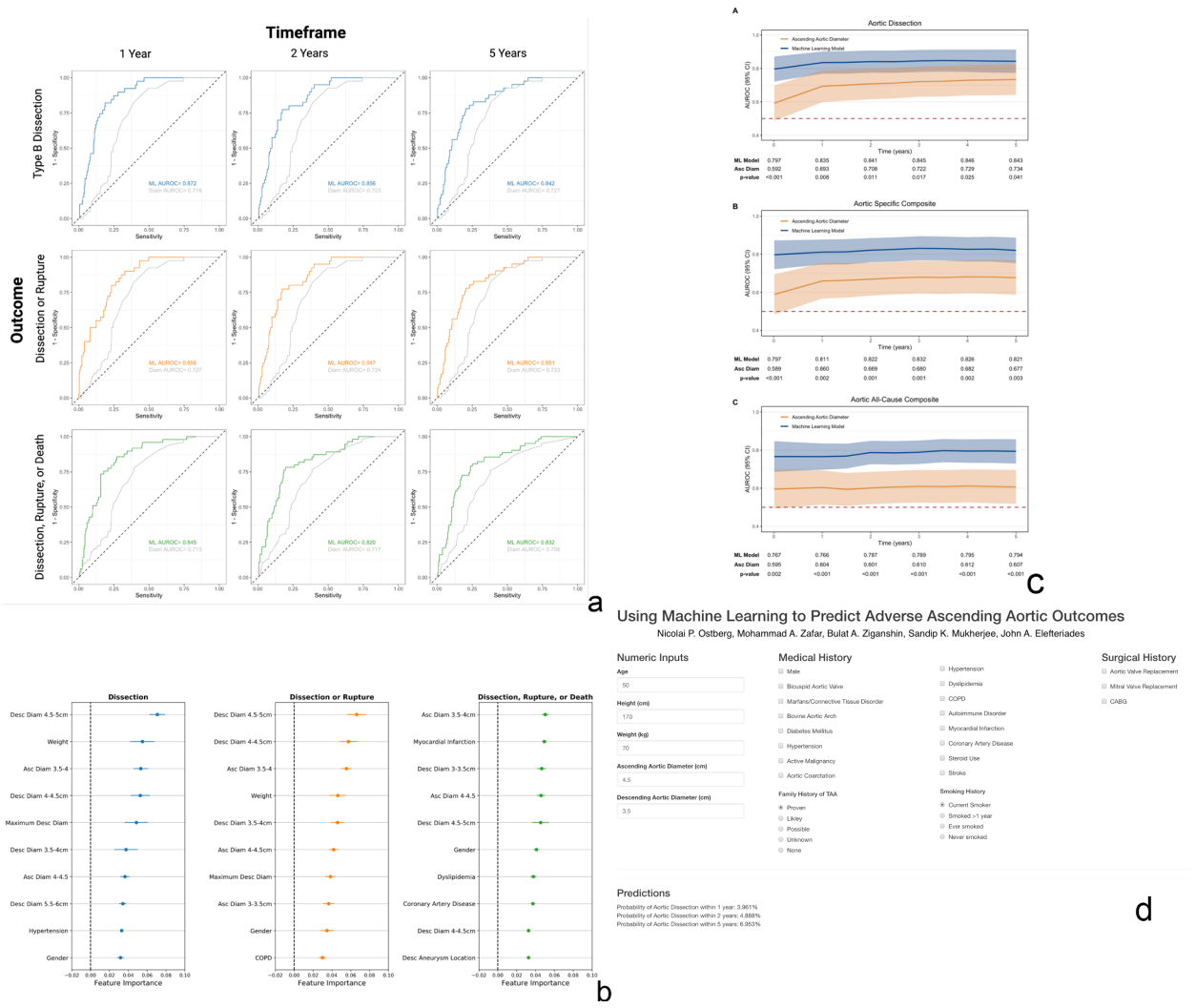

Figure 5a. **AUROC for each classifier using test data**. Colored lines represent the performance of the ML classifier, and gray lines represent the performance using maximal descending aortic diameter alone as a predictor. The black dashed line represents the performance of a random classifier. All ML classifiers outperformed maximum descending aortic diameter alone as a metric to predict outcomes in patients with descending thoracic aortic aneurysms. ML, Machine learning; AUROC, area under the receiver operator curve. Reproduced with permission from: Ostberg NP, Zafar MA, Mukherjee SK, Ziganshin BA, Elefteriades JA. A machine learning approach for predicting complications in descending and thoracoabdominal aortic aneurysms. J Thorac Cardiovasc Surg. 2022. Epub 20220111. doi: 10.1016/j.jtcvs.2021.12.045. PubMed PMID: 35120761. **5b**. Feature importance of each input variable for Bayesian Additive Regression Trees (BART) models at 5 years. Error bars represent ± standard deviation. Aortic diameter metrics remained among the most important features. This suggests the model is consistent with current clinical guidelines in that diameter is heavily weighted in the classification process. Features associated with atherosclerotic processes, such as myocardial infarction, hypertension, and gender, were also highly weighted, consistent with current understanding of pathology in the descending aorta as a heavily atherosclerotic phenomenon. COPD, Chronic obstructive pulmonary disease. Reproduced with permission from: Ostberg NP, Zafar MA, Mukherjee SK, Ziganshin BA, Elefteriades JA. A machine learning approach for predicting complications in descending and thoracoabdominal aortic aneurysms. J Thorac Cardiovasc Surg. 2022. Epub 20220111. doi: 10.1016/j.jtcvs.2021.12.045. PubMed PMID: 35120761. **5c**. Time dependent area under the receiver operator curves (AUROC) comparing machine learning (ML) models to ascending aortic diameter. The ML models outperformed aortic diameter across all time-points and endpoints when measured on the test set. Shaded regions represent 95% confidence intervals. The red-dashed line represents a random classifier with an AUROC of 0.5. **5d**. Computerized, interactive AI/ML-based calculator for determination of rupture/dissection risk of a specific aneurysm in a specific patient.

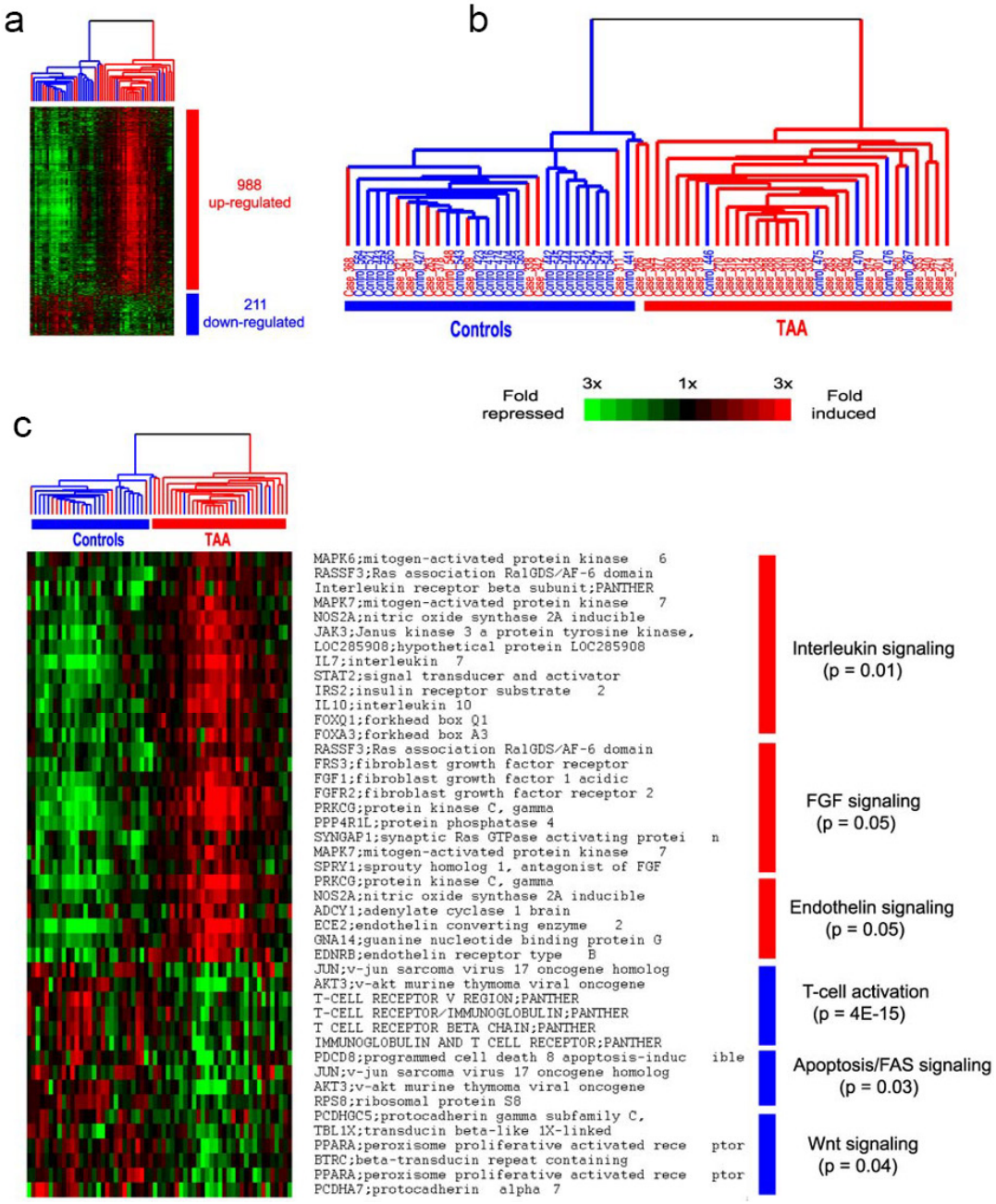

Figure 6. **Hierarchical clustering of 61 whole blood samples analyzed by Applied Biosystem Expression Arrays using the 1,199 differentially expressed genes determined by SAM analysis**. The level of expression of each gene in each sample, relative to the mean level of expression of that gene across all the samples, is represented using a red-black-green color scale as shown in the key (green: below mean; black: equal to mean; red: above mean). A. Scaled down representation of the entire cluster of the 1,199 signature genes and 61 whole blood samples. B. Experimental dendrogram displaying the clustering of the samples into two main branches: the TAA branch (red) and the control branch (blue) with a few exceptions. C. Gene expression pattern of representative genes within biological pathways that are statistically significantly over-represented (random overlapping p-value, 0.05) by the up-regulated (red bars) or the down-regulated (blue bars) signature genes of TAA. Reprinted with permission from: Yulei Wang Y, Barbacioru CC, Shiffman D, Balasubramanian S, Iakoubova O, Tranquilli M, Albornoz G, Blake J, Mehmet NN, Ngadimo D, Poulter K, Chan F, Samaha R, Elefteriades JA. PLoS One. 2007;10:e1050.doi:10.1371/journal.pone.0001050.g001.

(IMT), an early manifestation of atherosclerosis. We discovered that our ascending aneurysm patients had a significantly lower carotid IMT than control patients, independent of risk factors for atherosclerosis [41].

We then compared the prevalence of coronary artery disease and myocardial infarction in ascending aneurysm patients and controls, observing vanishingly low myocardial infarction rates and a significantly lower prevalence of coronary artery disease in the ascending aortic aneurysm group [42].

Finally, we compared low density lipoprotein levels in our ascending aneurysm patients to a normal population via a propensity score matched case-control study [43]. We found that low density lipoprotein levels were inversely correlated with the presence of ascending aneurysm, congruent with our previous three observations of protection from atherosclerosis in ascending aneurysm patients.

Therefore, it appears that the mutations that cause the aneurysm, while pro-aneurysmal, are also anti-atherogenic.

SPECIFIC FINDINGS AND INSIGHTS ENABLED BY OUR *MODERN* "BIG DATA" EFFORTS

This section presents our Yale Aortic Institute efforts that use Machine Learning/Artificial Intelligence for scientific investigations in aortic disease. Some of our findings in this realm have been published, some are currently submitted but not yet published, and others are in progress and "future pointing" regarding our research efforts.

Such analyses were not feasible even by the advanced conventional statistics employed earlier in our experience.

The Big Data machine learning/artifical intelligence approaches have the great advantage for our work of being able to detect *any type* of relationship between variables—not just linear or exponential, or the like. Of course, the corresponding drawback is the loss of understanding of "what is actually happening" to cause the newly demonstrated relationship.

Machine learning models for thoracic aortic aneurysm risk prediction: **outperforming traditional criteria**. Artificial intelligence and machine learning use in the medical field has burgeoned over the last decade, resulting in fascinating applications, from predicting hospital mortality using raw electronic health record data, to diagnosing diabetic retinopathy from retinal images [44,45]. The ability of machine learning to recognize complex patterns and interactions and to make connections and inferences beyond human perception can augment physician capabilities and improve patient care. We have described the potential applications of machine learning in the field of cardiothoracic surgery [5] and applied machine learning models to our database in order to refine our risk prediction capabilities.

Although aortic diameter is a powerful and well validated morphological predictor of adverse events in the thoracic aorta, it is by no means perfect: a substantial number of dissections occur below the 5.0 and 5.5 cm intervention thresholds [36]. Therefore, drawing on the wealth of information from our database, we developed machine learning based prediction models that factor in multiple patient characteristics above and beyond diameter to compute adverse aortic event risk. We can conceptualize these machine learning models as a "black box" that will take in various patient-specific input variables and will output the fine-tuned probability of an associated outcome like dissection, rupture, or a composite endpoint. Clinicians can then use this information to guide surgical decision making and patient counselling.

Our first study was based on over 1,000 descending thoracic and thoracoabdominal aortic aneurysm patients, encompassing 44 variables to predict three outcomes (dissection, dissection or rupture, and dissection, rupture, or death) within 1, 2, or 5 years [6]. Thus, a total of nine endpoints were constructed. Six different machine learning classifiers (generalized additive model, random forest, K nearest neighbor classifier, support vector machine, neural network, and Bayesian Additive Regression Trees (BART)) were employed, and a 70/30 train/test split was carried out. Each model's performance was evaluated via area under the receiver operator curve (AUROC). A total of 54 separate models were trained on the training set, using six different models across the three different end points at three different timepoints. An AUROC was calculated for each model using the testing set.

Overall, the BART model performed best across the modeling tasks, but the other models also emerged as the best performing classifier on at least one outcome. All machine learning models outperformed descending aortic diameter (Figure 5a) and height/body surface area indexed diameter across all end points. A feature importance analysis of each input variable revealed that aortic diameter remained the most important feature, but other features such as sex, hypertension, patient weight, and myocardial infarction were also heavily weighted (Figure 5b). Thus, the additive benefit of factoring in these various clinical characteristics likely improved the machine learning model performance, as depicted in the AUROC analysis in Figure 5a.

The machine learning models consistently outperform traditional statistical methods based on diameter alone (Figure 5c) and diameter-based indices in predicting adverse events in the ascending aorta.

The automated calculator generated by this machine

learning/artificial intelligence work—based on clinical data on over 2,500 patients with ascending thoracic aortic aneurysm—is presented in Figure 5d. A number of patient variables are entered by the clinician caring for the patient—including patient age and height, aneurysm dimensions, and medical, family, and smoking history—and a precise percentage yearly risk of aortic rupture or dissection is output by the program.

While it is reassuring that aortic diameter, the most widely used, easily accessible, and closely studied parameter, remains an important predictor of adverse events, machine learning models enhance risk prognostication in thoracic aortic aneurysm patients by integrating important non-diameter variables.

Our team has also been involved in developing an artificial intelligence-based platform deployed in the Yale University emergency radiology system that automatically and independently diagnoses the catastrophic event of aortic dissection from CT scans as soon as they exit the CT scanning machine—*before they are even seen by a radiologist*. The computer alerts the pertinent physicians and surgeons and the operating room team that an emergency operation is looming. Critical minutes are saved, and life preservation enhanced.

Genetic testing for thoracic aortic aneurysm and dissection and discovery of novel causative genes. As we outlined in our 2008 article in the *YJBM*, ascending thoracic aortic aneurysms are largely genetically mediated and are *not* related to traditional atherosclerotic risk factors [9]. We observed that dissections within families cluster by age, familial dissections occur at an earlier age than sporadic dissections, and a dissection in the family imparts a three times higher risk of dissection in first degree relatives [46,47]. We therefore recommend screening all first-degree relatives of aneurysm patients, a policy also advocated in the 2022 US guidelines [20]. Furthermore, if there is a patient with a modestly sized ascending aneurysm in clinic and there has already been a dissection in the family, we recommend prompt operative repair because it is only a matter of time before they will dissect.

To date, 67 TAA- and dissection-related genes have been identified. Our team regularly publishes a gene update with a graphic that depicts the size at which the aorta should be operated on for various mutations [48]. Our Institute also offers routine clinical genetic testing via WES to all our patients. We have thus far sequenced almost 2,000 patients. We find variants in known TAA risk genes in approximately 30% of patients, but, interestingly, of the 70% of patients in whom no actionable variants are identified, 40% have a positive family history, indicating that there are likely many more genes responsible for this disease that need to be identified and discovered [49].

In collaboration with colleagues at Columbia University, we have analyzed mountains of genetic data at our disposal (~45,000,000 letters of genetic data per patient) to continue the hunt for novel thoracic aortic aneurysm and dissection genes. These efforts, not yet reported, are bearing fruit.

Phenotypic genetic characterization by Artificial Intelligence. In collaboration with scientists at Emerge (SA), we have been able to make highly accurate genetic diagnoses by evaluation of facial features by Artificial Intelligence. These remarkable findings have just been submitted as a primary scientific study by our team.

Panel of RNAs "detects" thoracic aortic aneurysm. To be able to determine which individuals in the general population harbor or are susceptible to TAA would represent a tremendous advance in aortic care. In 2007, together with Dr. Olga Iakoubova of Celera Diagnostics (Celera had just mapped the human genome in 2009); we assessed serum levels of 33,0000 RNAs. We isolated a panel of 41 RNAs that could determine with a high degree of accuracy whether a given patient harbored a TAA. This analysis was done via complex (but traditional) Significance Analysis of Microarray (SAM) (Figure 6).

Before proceeding to clinical application, we are currently seeking to replicate the significance of the prior findings in a large, independent group of patients. The current analysis is being done via machine learning/artificial intelligence techniques within our Yale University network.

CONCLUSIONS

The "Big Data" that became available to our Aortic Institute team via compulsive collection of clinical information from a vigorous aortic care enterprise has enabled many important findings in the natural behavior of thoracic aortic aneurysm. This data included in-depth clinical parameters as well as copious genetic sequencing information. Multiple direct clinical correlates, principles, and guidelines have resulted from precise statistical and AI-based interpretation of this data. These have enhanced clinical care substantially. This experience illustrates vividly the progress that can be made when clinicians amass "Big Data" repositories and then collaborate with data scientists in their interpretation.

REFERENCES

1. Wu J, Zhao R, Zhuang D, Zhu J, Zheng H, Chen J. The recent 10-year landscape of aortic dissection research: a bibliometric analysis. J Thorac Dis. 2021 Mar;13(3):1592–602.
2. Elefteriades JA. Beating a sudden killer. Sci Am. 2005 Aug;293(2):64–71.
3. Rizzo JA, Coady MA, Elefteriades JA. Procedures for

estimating growth rates in thoracic aortic aneurysms. J Clin Epidemiol. 1998 Sep;51(9):747–54.
4. Biesecker LG, Green RC. Diagnostic clinical genome and exome sequencing. N Engl J Med. 2014 Jun;370(25):2418–25.
5. Ostberg NP, Zafar MA, Elefteriades JA. Machine learning: principles and applications for thoracic surgery. Eur J Cardiothorac Surg. 2021 Jul;60(2):213–21.
6. Ostberg NP, Zafar MA, Mukherjee SK, Ziganshin BA, Elefteriades JA. A machine learning approach for predicting complications in descending and thoracoabdominal aortic aneurysms. J Thorac Cardiovasc Surg. Epub. 2022;20220111: https://doi.org/10.1016/j.jtcvs.2021.12.045.
7. Liang L, Liu M, Martin C, Elefteriades JA, Sun W. A machine learning approach to investigate the relationship between shape features and numerically predicted risk of ascending aortic aneurysm. Biomech Model Mechanobiol. 2017;16(5):1519-33. Epub 20170406. https://doi.org/10.1007/s10237-017-0903-9.
8. Liang L, Liu M, Elefteriades J, Sun W. Synergistic Integration of Deep Neural Networks and Finite Element Method with Applications for Biomechanical Analysis of Human Aorta. bioRxiv. 2023. Epub 20230405. https://doi.org/10.1101/2023.04.03.535423.
9. Elefteriades JA. Thoracic aortic aneurysm: reading the enemy's playbook. Yale J Biol Med. 2008 Dec;81(4):175–86.
10. Coady MA, Rizzo JA, Hammond GL, Mandapati D, Darr U, Kopf GS, et al. What is the appropriate size criterion for resection of thoracic aortic aneurysms? J Thorac Cardiovasc Surg. 1997 Mar;113(3):476–91.
11. Coady MA, Rizzo JA, Hammond GL, Kopf GS, Elefteriades JA. Surgical intervention criteria for thoracic aortic aneurysms: a study of growth rates and complications. Ann Thorac Surg. 1999 Jun;67(6):1922–6.
12. Davies RR, Goldstein LJ, Coady MA, Tittle SL, Rizzo JA, Kopf GS, et al. Yearly rupture or dissection rates for thoracic aortic aneurysms: simple prediction based on size. Ann Thorac Surg. 2002;73(1):17-27; discussion -8. https://doi.org/10.1016/S0003-4975(01)03236-2.
13. Hiratzka LF, Bakris GL, Beckman JA, Bersin RM, Carr VF, Casey DE Jr, et al.; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. American Association for Thoracic Surgery; American College of Radiology; American Stroke Association; Society of Cardiovascular Anesthesiologists; Society for Cardiovascular Angiography and Interventions; Society of Interventional Radiology; Society of Thoracic Surgeons; Society for Vascular Medicine. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM Guidelines for the diagnosis and management of patients with thoracic aortic disease. A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology,American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons,and Society for Vascular Medicine. J Am Coll Cardiol. 2010 Apr;55(14):e27–129.
14. Erbel R, Aboyans V, Boileau C, Bossone E, Bartolomeo RD, Eggebrecht H, et al.; The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC). 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases: document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. Eur Heart J. 2014 Nov;35(41):2873–926.
15. Elefteriades JA, Mukherjee SK, Mojibian H. Discrepancies in Measurement of the Thoracic Aorta: JACC Review Topic of the Week. J Am Coll Cardiol. 2020 Jul;76(2):201–17.
16. Ban E, Kalogerakos PD, Khosravi R, Ziganshin BA, Ellauzi H, Ramachandra AB, et al. Extended law of laplace for measurement of the cloverleaf anatomy of the aortic root. Int J Cardiovasc Imaging. 2023 Jul;39(7):1345–56.
17. Peterss S, Charilaou P, Ziganshin BA, Elefteriades JA. Assessment of survival in retrospective studies: the Social Security Death Index is not adequate for estimation. J Thorac Cardiovasc Surg. 2017 Apr;153(4):899–901.
18. Elefteriades JA, Rizzo JA, Zafar MA, Ziganshin BA. Ascending aneurysmectomy: Should we shift to the left? J Thorac Cardiovasc Surg. Epub. 2022;20220806: https://doi.org/10.1016/j.jtcvs.2022.07.033.
19. Ziganshin BA, Zafar MA, Elefteriades JA. Descending threshold for ascending aortic aneurysmectomy: is it time for a "left-shift" in guidelines? J Thorac Cardiovasc Surg. 2019 Jan;157(1):37–42.
20. Isselbacher EM, Preventza O, Hamilton Black J 3rd, Augoustides JG, Beck AW, Bolen MA, et al. ACC/AHA Guideline for the Diagnosis and Management of Aortic Disease: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. Circulation. 2022;146(24):e334-e482. Epub. 2022;20221102: https://doi.org/10.1161/CIR.0000000000001106.
21. Davies RR, Gallo A, Coady MA, Tellides G, Botta DM, Burke B, et al. Novel measurement of relative aortic size predicts rupture of thoracic aortic aneurysms. Ann Thorac Surg. 2006 Jan;81(1):169–77.
22. Zafar MA, Li Y, Rizzo JA, Charilaou P, Saeyeldin A, Velasquez CA, et al. Height alone, rather than body surface area, suffices for risk estimation in ascending aortic aneurysm. J Thorac Cardiovasc Surg. 2018 May;155(5):1938–50.
23. Demertzis S, Grego S. Predictability of acute aortic dissection. A dream come true? J Thorac Cardiovasc Surg. 2019 Jun;157(6):e324.
24. Cheung C, Bernardo AS, Trotter MW, Pedersen RA, Sinha S. Generation of human vascular smooth muscle subtypes provides insight into embryological origin-dependent disease susceptibility. Nat Biotechnol. 2012;30(2):165-73. Epub 20120115. https://doi.org/10.1038/nbt.2107.
25. Kalogerakos PD, Zafar MA, Li Y, Mukherjee SK, Ziganshin BA, Rizzo JA, et al. Root Dilatation Is More Malignant Than Ascending Aortic Dilation. J Am Heart Assoc. 2021 Jul;10(14):e020645.
26. Hoffman JI, Kaplan S. The incidence of congenital heart disease. J Am Coll Cardiol. 2002 Jun;39(12):1890–900.
27. Braverman AC, Güven H, Beardslee MA, Makan M, Kates AM, Moon MR. The bicuspid aortic valve. Curr Probl

Cardiol. 2005 Sep;30(9):470–522.
28. Davies RR, Kaple RK, Mandapati D, Gallo A, Botta DM Jr, Elefteriades JA, et al. Natural history of ascending aortic aneurysms in the setting of an unreplaced bicuspid aortic valve. Ann Thorac Surg. 2007 Apr;83(4):1338–44.
29. Michelena HI, Desjardins VA, Avierinos JF, Russo A, Nkomo VT, Sundt TM, et al. Natural history of asymptomatic patients with normally functioning or minimally dysfunctional bicuspid aortic valve in the community. Circulation. 2008 May;117(21):2776–84.
30. Michelena HI, Khanna AD, Mahoney D, Margaryan E, Topilsky Y, Suri RM, et al. Incidence of aortic complications in patients with bicuspid aortic valves. JAMA. 2011 Sep;306(10):1104–12.
31. Zafar MA, Wu J, Vinholo TF, Li Y, Papanikolaou D, Ellauzi H, et al. Bicuspid aortopathy does not require earlier surgical intervention. J Thorac Cardiovasc Surg. 2023 Apr;20230421:S0022-5223(23)00341-0. https://doi.org/10.1016/j.jtcvs.2023.04.017.
32. Borger MA, Fedak PW, Stephens EH, Gleason TG, Girdauskas E, Ikonomidis JS, et al. The American Association for Thoracic Surgery consensus guidelines on bicuspid aortic valve-related aortopathy: full online-only version. J Thorac Cardiovasc Surg. 2018 Aug;156(2):e41–74.
33. Elefteriades JA, Farkas EA. Thoracic aortic aneurysm clinically pertinent controversies and uncertainties. J Am Coll Cardiol. 2010 Mar;55(9):841–57.
34. Maleszewski JJ. Inflammatory ascending aortic disease: perspectives from pathology. J Thorac Cardiovasc Surg. 2015;149(2 Suppl):S176-83. Epub 20140801. https://doi.org/10.1016/j.jtcvs.2014.07.046.
35. Zafar MA, Chen JF, Wu J, Li Y, Papanikolaou D, Abdelbaky M, et al.; Yale Aortic Institute Natural History Investigators. Natural history of descending thoracic and thoracoabdominal aortic aneurysms. J Thorac Cardiovasc Surg. 2021 Feb;161(2):498–511.e1.
36. Perez ZG, Zafar MA, Velasco JJ, Sonsino A, Ellauzi H, John C, et al. Aortic Size at the Time of Type A and Type B Dissections. Ann Thorac Surg. 2023 Aug;116(2):262–8.
37. Wu J, Zafar M, Qiu J, Huang Y, Chen Y, Yu C, et al. A systematic review and meta-analysis of isolated abdominal aortic dissection. J Vasc Surg. 2019 Dec;70(6):2046–2053.e6.
38. Chen JF, Zafar MA, Wu J, Li Y, Rizzo JA, Papanikolaou D, et al. Increased Virulence of Descending Thoracic and Thoracoabdominal Aortic Aneurysms in Women. Ann Thorac Surg. 2021 Jul;112(1):45–52.
39. Wu J, Zafar MA, Li Y, Saeyeldin A, Huang Y, Zhao R, et al. Ascending Aortic Length and Risk of Aortic Adverse Events: The Neglected Dimension. J Am Coll Cardiol. 2019 Oct;74(15):1883–94.
40. Achneck H, Modi B, Shaw C, Rizzo J, Albornoz G, Fusco D, et al. Ascending thoracic aneurysms are associated with decreased systemic atherosclerosis. Chest. 2005 Sep;128(3):1580–6.
41. Hung A, Zafar M, Mukherjee S, Tranquilli M, Scoutt LM, Elefteriades JA. Carotid intima-media thickness provides evidence that ascending aortic aneurysm protects against systemic atherosclerosis. Cardiology. 2012;123(2):71–7.
42. Chau K, Elefteriades JA. Ascending thoracic aortic aneurysms protect against myocardial infarctions. Int J Angiol. 2014 Sep;23(3):177–82.
43. Weininger G, Ostberg N, Shang M, Zafar M, Ziganshin BA, Liu S, et al. Lipid profiles help to explain protection from systemic atherosclerosis in patients with ascending aortic aneurysm. J Thorac Cardiovasc Surg. 2021; https://doi.org/10.1016/j.jtcvs.2021.09.031.
44. Rajkomar A, Oren E, Chen K, Dai AM, Hajaj N, Hardt M, et al. Scalable and accurate deep learning with electronic health records. NPJ Digit Med. 2018 May;1(1):18.
45. Ting DS, Cheung CY, Lim G, Tan GS, Quang ND, Gan A, et al. Development and Validation of a Deep Learning System for Diabetic Retinopathy and Related Eye Diseases Using Retinal Images From Multiethnic Populations With Diabetes. JAMA. 2017 Dec;318(22):2211–23.
46. Chou AS, Ma WG, Mok SC, Ziganshin BA, Peterss S, Rizzo JA, et al. Do Familial Aortic Dissections Tend to Occur at the Same Age? Ann Thorac Surg. 2017 Feb;103(2):546–50.
47. Ma WG, Chou AS, Mok SC, Ziganshin BA, Charilaou P, Zafar MA, et al. Positive family history of aortic dissection dramatically increases dissection risk in family members. Int J Cardiol. 2017 Aug;240:132–7.
48. Faggion Vinholo T, Brownstein AJ, Ziganshin BA, Zafar MA, Kuivaniemi H, Body SC, et al. Genes Associated with Thoracic Aortic Aneurysm and Dissection: 2019 Update and Clinical Implications. Aorta (Stamford). 2019 Jun;7(4):99–107.
49. Ziganshin BA, Bailey AE, Coons C, Dykas D, Charilaou P, Tanriverdi LH, et al. Routine Genetic Testing for Thoracic Aortic Aneurysm and Dissection in a Clinical Setting. Ann Thorac Surg. 2015 Nov;100(5):1604–11.